Electrophysiologic Study-Guided Amiodarone for Sustained Ventricular Tachyarrhythmias Associated With Structural Heart Diseases

Takeshi Aiba, MD; Kenichiro Yamagata, MD; Wataru Shimizu, MD; Atsushi Taguchi, MD; Kazuhiro Satomi, MD; Takashi Noda, MD; Hideo Okamura, MD; Kazuhiro Suyama, MD; Naohiko Aihara, MD; Shiro Kamakura, MD; Takashi Kurita, MD

Circulation Journal
Vol. 72 No. 1 January 2008
(Pages 88–93)

Circ J 2008; **72:** 88–93

Electrophysiologic Study-Guided Amiodarone for Sustained Ventricular Tachyarrhythmias Associated With Structural Heart Diseases

Takeshi Aiba, MD; Kenichiro Yamagata, MD; Wataru Shimizu, MD; Atsushi Taguchi, MD; Kazuhiro Satomi, MD; Takashi Noda, MD; Hideo Okamura, MD; Kazuhiro Suyama, MD; Naohiko Aihara, MD; Shiro Kamakura, MD; Takashi Kurita, MD

Background Although an electrophysiologic study (EPS) and Holter-monitoring are often helpful in evaluating the efficacy of antiarrhythmic drugs in patients with ventricular tachyarrhythmias (ventricular tachycardia/fibrillation (VT/VF)), the efficacy of EPS- or Holter-guided oral amiodarone therapy in Japanese patients is still unclear.

Methods and Results EPS was performed 1 month after starting amiodarone, and Holter-monitoring was recorded before and 1 month after amiodarone in 188 patients with sustained VT/VF because of structural heart diseases. In spite of the judgment of EPS (n=89) or Holter (n=75), all patients continued amiodarone. Patients were followed up to 3 years and the primary endpoint was VT/VF recurrence and secondary endpoint was death by all cause. Kaplan-Meier estimated the risk of VT/VF recurrence was significantly smaller with EPS-guided amiodarone ($p<0.01$) but not with Holter-guided amiodarone. Multivariate Cox hazard analysis revealed that EPS-guided amiodarone was an independent factor suppressing the recurrence of VT/VF ($p<0.05$, 95% confidence interval=0.15 to 0.96). In the subgroup analysis, EPS-guided amiodarone was effective in patients with relatively well-preserved left ventricular ejection fraction (LVEF ≥0.30) but not in patients with lower LVEF (LVEF <0.30).

Conclusion EPS-guided amiodarone was useful for preventing recurrence of VT/VF in patients with a relatively well-preserved LVEF, but not always beneficial in patients with a lower LVEF. (*Circ J* 2008; **72:** 88–93)

Key Words: Amiodarone; Electrophysiologic study; Holter monitoring; Ventricular fibrillation; Ventricular tachycardia

Ventricular tachyarrhythmias are critically important in the prognosis of patients with structural heart diseases. Amiodarone is one of the most advocated antiarrhythmic drugs available for preventing the recurrence of ventricular tachycardia (VT), ventricular fibrillation (VF), thereby reducing total mortality in patients with VT/VF![1–4] Although an electrophysiologic study (EPS) and Holter monitoring are performed to evaluate the efficacy of antiarrhythmic drugs, oral amiodarone is often prescribed empirically because the antiarrhythmic effect as guided by EPS or Holter monitoring is controversial![5–9] Recent clinical trials have shown that an implantable cardioverter defibrillator (ICD) is clearly superior to amiodarone for preventing sudden arrhythmic death![10–13] but cannot prevent the recurrence of VT/VF and sometimes gives an intolerable shock to the patient. Therefore, it is still important to clarify how to optimize amiodarone and/or ICD therapies in patients with sustained VT/VF and structural heart diseases![14,15]

On the other hand, patients with a lower left ventricular ejection fraction (LVEF) derive significantly more benefit from ICD therapy than those with a better preserved LVEF![16–18] Moreover, a recent randomized study reported that amiodarone had no favorable effect on survival but that ICD therapy reduced overall mortality by 23% in patients with congestive heart failure and LVEF <35%![19] Therefore, a cardiac function parameter, such as LVEF, is important in determining the prognosis of patients with sustained VT/VF. The goals of this study were: (1) to evaluate whether or not EPS- or Holter monitoring-guided therapy can stratify the risk of VT/VF recurrence after oral amiodarone, and (2) to investigate the extent to which specific patients subgroups benefit differently from amiodarone therapy.

Methods

Patients

This study retrospectively analyzed 400 patients who had been treated with oral amiodarone at the National Cardiovascular Center (Suita, Japan) from 1990 to 2004. All patients had a history of symptomatic sustained VT/VF because of structural heart diseases. We excluded 212 patients with a LVEF >0.50, treated with amiodarone for nonsustained VT or atrial arrhythmias, or who had undergone radiofrequency catheter ablation or surgical procedures for VT/VF. Therefore, this study registered 188 patients (mean age, 60±12 years; 149 males), which included 77 patients with previous myocardial infarction, 61 with dilated cardio-

(Received November 2, 2006; revised manuscript received August 21, 2007; accepted September 13, 2007)

Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan

Mailing address: Takashi Kurita, MD, Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: kuritat@hsp.ncvc.go.jp

Table 1 Patients' Characteristics

	Overall	EPS-post amiodarone		EPS (−)
		VT (−)	VT (+)	
n	188	27	62	99
Age (years)	60±12	59±9	58±11	61±14
Sex (male, %)	149 (79)	22 (81)	48 (77)	80 (81)
LVEF (%)	30±12	30±11	34±11	28±12*
Structural heart disease (%)				
Old MI	77 (41)	14 (52)	24 (39)	39 (39)
DCM	61 (33)	7 (26)	18 (29)	36 (36)
HCM	8 (4)	0 (0)	4 (6)	4 (4)
ARVC	16 (9)	1 (4)	6 (10)	9 (9)
Sarcoidosis	11 (6)	2 (7)	6 (10)	3 (3)
Valvular heart disease	12 (6)	1 (4)	3 (5)	8 (8)
Other	3 (1)	2 (7)	1 (1)	0 (0)
Presenting arrhythmias (%)				
Sustained VT	150 (80)	23 (85)	56 (91)	70 (71)
VF	26 (14)	4 (15)	2 (3)	21 (21)
Sustained VT and VF	12 (6)	0 (0)	4 (6)	8 (8)
VF total (%)	38 (20)	4 (15)	6 (9)	29 (29)*
ICD (%)	81 (43)	7 (26)	40 (65)**	34 (34)
Medication (%)				
ACEI	103 (55)	18 (67)	30 (48)	55 (55)
β-blocker	102 (55)	12 (44)	34 (55)	56 (57)
Digitalis	60 (32)	9 (33)	13 (21)	38 (38)

EPS, electrophysiological study; VT (−), VT or VF is not induced by EPS; VT (+), VT or VF is induced by EPS; LVEF, left ventricular ejection fraction; MI, myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; ACEI, angiotensin converting enzyme inhibitors.
**p<0.05 vs EPS-VT (+) group; ** p<0.05 vs EPS-VT (−) and EPS (−) group.*

myopathy, 16 with arrhythmogenic right ventricular cardiomyopathy, 8 with hypertrophic cardiomyopathy, and 11 with cardiac sarcoidosis. The mean LVEF of these patients was 30±12% (Table 1).

EPS and Holter Monitoring

After written informed consent was given, EPS was performed in the fasting, nonsedated state before (pre) and 1 month after (post) starting oral amiodarone. All other antiarrhythmic drugs were discontinued. The protocols of the programmed ventricular stimuli have been described in detail previously[4] In brief, up to 3 premature extrastimuli after an 8-beat stimulus drive were delivered from the right ventricular apex and outflow tract using a quadripolar-electrode catheter, and incremental ventricular stimulation with a constant cycle length. The stimulation protocol was terminated when sustained VT or VF was induced. The efficacy of amiodarone was determined by whether or not a run of VT >15 beats could be induced during EPS after starting amiodarone. Thus, we were not concerned about the inducibility of VT/VF before amiodarone therapy.

Twenty-four hours Holter electrocardiogram was recorded on magnetic tape before drug therapy, and repeated 1 month after administration of amiodarone and analyzed by computer to determine the frequency of arrhythmias. The efficacy of amiodarone by Holter recording was assessed by the criteria of the ESVEM trial[20] First, patients with total premature ventricular contractions (PVC) less than 300/day before amiodarone were excluded from the Holter judgment as an "undetermined" group. Therefore, patients with total PVCs more than 300/day before amiodarone and 70% reduction in the PVC count, 80% reduction in the PVC pair count, 90% reduction in the VT count, and absence of any runs of VT >15 beats were defined as "effective", but patients with no response to these criteria were defined as "ineffective".

Table 2 EPS and Holter Judgments

	EPS post amiodarone		EPS-post (−)
	VT (−)	VT (+)	
EPS pre amiodarone			
VT (−) (n=2)	1	0	1
VT (+) (n=37)	3	16	18
EPS-pre (−) (n=149)	23	46	80
Total (n=188)	27	62	99
Holter criteria			
Effective (n=37)	7	9	21
Ineffective (n=38)	7	10	21
Undetermined (n=113)	13	43	57

EPS-pre (−), EPS before amiodarone is not performed; EPS-post (−), EPS after amiodarone is not performed. Other abbreviations see in Table 1.

Follow-up After Amiodarone

Whether or not they had EPS or Holter monitoring, all patients continued treatment with amiodarone, the loading dose of which was 300 or 400 mg/day for 2 weeks followed by a maintenance dose of 150 or 200 mg/day. However, amiodarone was discontinued when critical side effects developed or it was obviously ineffective. All patients were followed up to 36 months and the primary endpoint was recurrence of VT/VF and the secondary endpoint was death from all causes. Implantation of an ICD was recommended in patients who were considered to be "ineffective" with amiodarone or had a history of syncope because of VT/VF.

Statistical Analysis

The continuous variables are expressed as mean±SD and were compared by an unpaired t-test when appropriate. Cumulative event rates were calculated by the Kaplan-

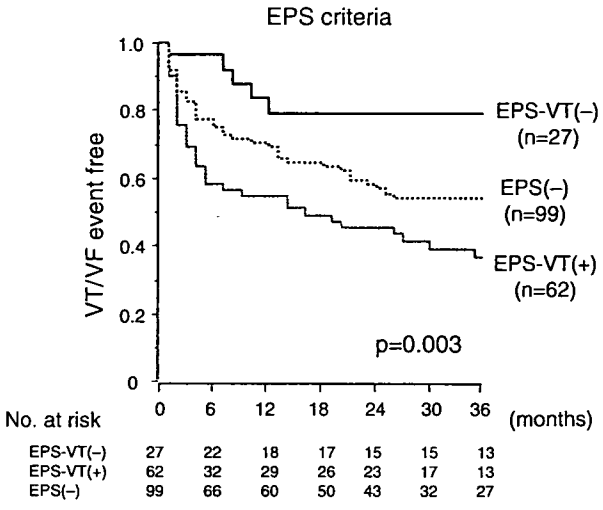

Fig 1. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by electrophysiological study (EPS) criteria. EPS stratified the risk of VT/VF recurrence after amiodarone. EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(−), patients with no inducible VT/VF by EPS after amiodarone; EPS(−), patients without EPS after amiodarone.

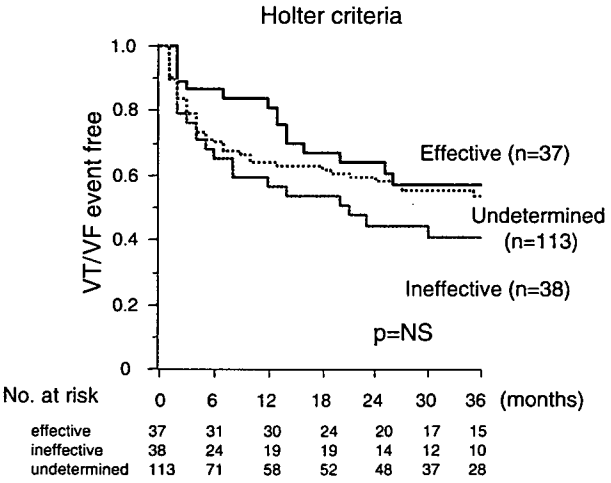

Fig 2. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by Holter-monitoring criteria. Holter-monitoring could not stratify the risk of VT/VF recurrence after amiodarone. Effective, patients judged amiodarone effective by Holter; Ineffective, patients judged amiodarone ineffective by Holter; Undetermined, patients excluded from the Holter judgment.

Table 3 Cox Hazard Regression Analysis of VT/VF Recurrence

	OR (95%CI)	*p value*
Age	*1.26 (0.80–1.99)*	*0.33*
Sex (male)	*0.93 (0.54–1.60)*	*0.78*
Basal disease (Old MI)	*0.75 (0.45–1.25)*	*0.27*
LVEF <30%	*1.47 (0.94–2.32)*	*0.09*
EPS post amiodarone		
VT (+)	*1.71 (1.07–2.75)*	*0.02*
VT (−)	*0.34 (0.15–0.96)*	*0.04*
Holter judgment		
Ineffective	*1.47 (0.87–2.50)*	*0.15*
Effective	*0.77 (0.42–1.43)*	*0.42*

Abbreviations as in Tables 1,2.

Meier method. The significance of the difference between treatment groups was assessed with the log-rank test. Cox regression analysis was performed on the patients' baseline characteristics to investigate and compare the influence of different variables. Statistical significance was established as $p<0.05$.

Results

EPS and Holter Monitoring

Table 2 summarizes the results of EPS and Holter monitoring. The EPS before amiodarone was performed in 39 patients, and induced VT/VF in 37 (95%). The EPS after amiodarone was performed in 89 patients, and could not induce VT/VF in 27 (30%) patients (EPS-VT(−) group), but still induced VT/VF in 62 (70%) patients (EPS-VT(+) group). The remaining 99 patients taking amiodarone without judgment by EPS were defined as EPS(−) group.

Holter monitoring before and after amiodarone treatment was recorded in 139 patients; however, 64 patients had less PVCs than the Holter evaluation before amiodarone (300/day). Therefore, the remaining 75 patients were judged as amiodarone effective (n=37) or ineffective (n=38) by Holter monitoring.

Follow-up

During the follow-up period of 23±13 (range 1–36) months, 82 (44%) patients had recurrence of VT. Moreover, 28 (20%) patients died during follow-up because of heart failure (n=8), sudden unexpected death (n=8), pneumonia (n=2), and unknown causes (n=10). Side-effects of amiodarone occurred in 39 (21%) patients, including hypothyroidism (n=20), proarrhythmia (n=5), pneumonia (n=11), leukocytopenia (n=1), and liver dysfunction (n=2). Amiodarone was discontinued in 13 (8%) patients because of serious side-effects.

Fig 1 illustrates the follow-up results of patients under the EPS criteria. Among those assigned to the EPS-VT(+) group, the rate of VT/VF recurrence was 45.6% and 63.9% at 1 and 3 years, respectively. Conversely, in the EPS-VT(−) group it was 21.3% and 21.3%, and for the EPS(−) group 31.0% and 46.6% at 1 and 3 year's follow-up, respectively. Therefore, the VT/VF recurrence risk after amiodarone was significantly lower in the order of EPS-VT(−), EPS(−), and EPS-VT(+) groups ($p<0.003$). Table 1 summarizes the clinical characteristics in the 3 groups. Age, sex, basal disease, and medication, except antiarrhythmic drugs, did not differ between them, although LVEF was lower in the EPS(−) group than in the EPS-VT(+) group (28±12% vs 34±11%; $p=0.01$), and VF incidence before amiodarone was higher in the EPS(−) group than in the EPS-VT(+) group (29% vs 9%; $p=0.01$). ICDs were consequently implanted in many of the EPS-VT(+) group compared with the EPS-VT(−) and EPS(−) groups (65% vs 26%, 34%, respectively; $p<0.05$).

Fig 2 illustrates the follow-up results under the Holter criteria. In the patients assigned to the effective group, the VT/VF recurrence rates were 19.1% and 42.8% (1 and 3 years, respectively), whereas in the ineffective group, they were 43.4% and 59.6% (1 and 3 years, respectively) (p=NS). Therefore, Holter monitoring cannot stratify the risk of VT/VF recurrence after amiodarone.

Table 3 shows the results of multivariate Cox hazard regression analysis for the recurrence of VT/VF after amiodarone. The clinical factors, age, gender, basal disease

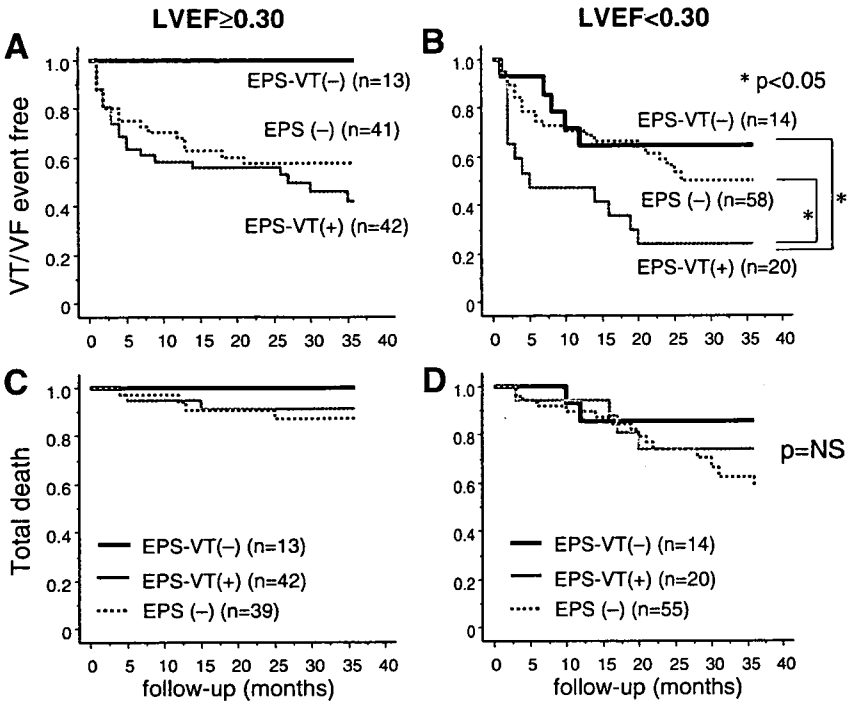

Fig 3. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) and total death after amiodarone therapy in different range of left ventricular ejection fraction (LVEF). Electrophysiological study (EPS) judgment could classify the risk of recurrent VT/VF and mortality after amiodarone in patients with LVEF ≥30% (A and C, respectively) but not in those with LVEF <30% (B and D, respectively). EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(−), patients with no inducible VT/VF by EPS after amiodarone; EPS(−), patients without EPS after amiodarone.

(myocardial infarction) and Holter judgments were not related to VT/VF recurrence. The independent clinical factors for VT/VF recurrence were inducibility of VT/VF by EPS after amiodarone (odds ratio (OR) 1.71, 95% confidence interval (CI) 1.07–2.75, p=0.02). Lower LVEF (<30%) increased the risk of VT/VF recurrence but not significantly (OR 1.47, 95%CI 0.94–2.32, p=0.09).

EPS-Guided AmiodaroneTherapy and LVEF

Because of the possibility of lower LVEF increasing risk of VT/VF recurrence after amiodarone, we evaluated the EPS-guided amiodarone therapy in subgroups. Therefore, among the patients with relatively preserved LVEF (≥30%) (n=94), there was no VT/VF recurrence in the EPS-VT(−) group, whereas the rates of VT/VF recurrence for the EPS-VT(+) group were 42.1% and 58.5%, and those for the EPS(−) group were 32.3% and 42.7% (at 1 and 3 years, respectively) (Fig 3A). Thus, the risk of VT/VF recurrence was significantly lower in the EPS-VT(−) group compared with the EPS-VT(+) and EPS(−) groups. In contrast, among patients with lower LVEF (<30%) (n=91), the rates of VT/VF recurrence for the EPS-VT(+) group were significantly higher (58.6% and 76.4% at 1 and 3 years, respectively) than those for the EPS-VT(−) (35.7% and 35.7%) and EPS(−) group (30.0% and 51.0%, respectively) (p<0.05), whereas there was no significant difference in the recurrence rate between the EPS-VT(−) and the EPS(−) groups (Fig 3B). Furthermore, in patients with LVEF ≥30%, no patients died in the EPS-VT(−) group, whereas 3 of 42 patients in the EPS-VT(+) group and 4 of 39 patients in the EPS(−) group died during follow-up (Fig 3C). However, in patients with LVEF<30%, 2 of 14 patients in the EPS-VT(−), 4 of 20 patients in the EPS-VT(+) and 15 of 55 patients in the EPS(−) group died during follow-up (p=NS) (Fig 3D).

Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for recurrence of VT/VF for Holter, EPS pre-post and EPS-post amiodarone therapy. The EPS judgment showed lower sensitivity but significantly higher specificity for recurrence of VT/VF, especially in patients with LVEF ≥30%.

Table 4 Predictors of Arrhythmic Events

	SNS	*SPC*	*PPV*	*NPV*	*ACC*
Holter-judgment (n=75)	*55*	*59*	*58*	*56*	*57*
EPS pre-post amiodarone (n=19)	*69*	*100*	*100*	*38*	*74*
EPS post amiodarone (n=89)	*59*	*81*	*88*	*46*	*66*
LVEF ≥30% (n=55)	*52*	*100*	*100*	*35*	*62*
LVEF <30% (n=34)	*70*	*64*	*74*	*60*	*68*

SNS, sensitivity; SPC, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy. Other abbreviations as in Table 1.

ICD and LVEF

We further analyzed the relationship between ICD and LVEF in patients treated with amiodarone. As shown in Fig 4A, the mortality of patients treated with amiodarone plus ICD did not differ between patients with higher (≥30%) and lower (<30%) LVEF. However, among patients with no ICD (amiodarone only) (Fig 4B), patients with LVEF ≥30% had a similar mortality to those with ICD, but patients with LVEF<30% had a significant worse mortality than the patients with higher LVEF (p=0.01). Therefore, patients with moderate to severe LV dysfunction achieved the greatest benefit from ICD therapy.

Discussions

Major Findings

This study retrospectively demonstrated the long-term effect of EPS-guided oral amiodarone therapy in Japanese patients with a history of life-threatening ventricular tachyarrhythmias because of structural heart diseases. EPS-guided amiodarone could reduce the recurrence of VT, especially in patients with relatively preserved (≥30%)

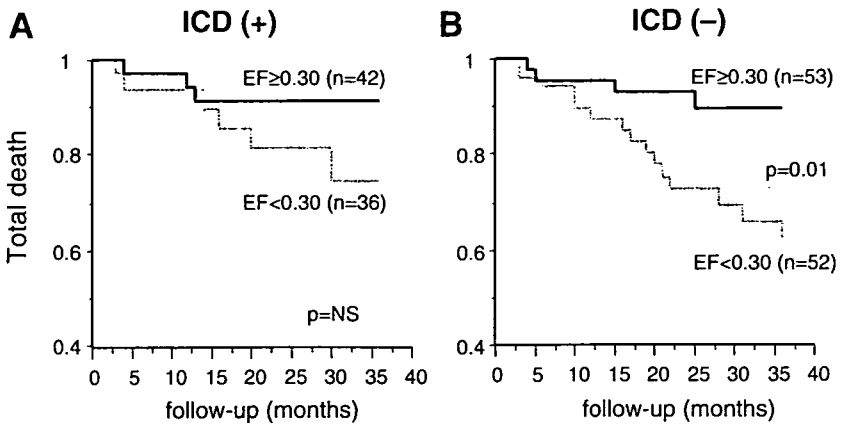

Fig 4. Cumulative risk of total death after amiodarone therapy in patients with implantable cardioverter defibrillator (ICD) (ICD(+)) and without ICD (ICD(−)). Higher (≥30%) and lower (<30%) left ventricular (LV) ejection fraction (EF) have similar risk for mortality in ICD(+) patients (A), but higher LVEF has significantly smaller risk of mortality than lower LVEF in ICD(−) patients (B).

LVEF, but was not always beneficial in patients with lower (<30%) LVEF. Therefore, amiodarone-treated patients with lower LVEF but not an implanted ICD remain at higher risk of sudden death.

EPS or Holter-Guided Amiodarone

Previous studies showed that EP-guided amiodarone therapy was useful for predicting recurrence of VT in patients at high risk for sudden cardiac death[5,7,8,21] McGovern et al reported that the sensitivity, specificity and accuracy of EP testing for recurrent VT was 58%, 91% and 67%, respectively[22] Those data coincide with our results showing that EPS-guided therapy has low sensitivity (59%), but high specificity (81%), for recurrence of VT after amiodarone. Moreover, this low sensitivity and high specificity of EP testing is more prominent in patients with LVEF ≥30% (52% and 100%, respectively) (Table 4). In this study, there were a small number of patients available for checking inducibility of VT before amiodarone, but the results of EPS-guided amiodarone are similar to those previously reported. Thus, it is not necessary to perform an EPS before starting amiodarone, and patients with LVEF ≥30% and non-inducible VT according to he EPS after amiodarone may remain free from recurrence of VT.

The ESVEM study showed that there was no significant difference between EPS and Holter monitoring in the probability of arrhythmic events occurring after antiarrhythmic drugs[20] However, that study mainly examined the effectiveness of class I antiarrhythmic drugs, not amiodarone. The efficacy of amiodarone by Holter monitoring is also controversial. Veltri et al reported that Holter monitoring could predict the long-term efficacy of amiodarone[6] Nasir et al showed that amiodarone strongly suppressed PVCs but this suppression did not predict clinical outcome[23] Our finding that a Holter judgment could not predict the recurrence of VT after amiodarone may have resulted because (1) there was a smaller number of patients undergoing Holter monitoring before and after amiodarone, (2) twenty-four hours recording cannot detect the number of PVCs or VT precisely, and (3) the apparent number of PVCs might have no relation to the trigger of critical VT or VF. In this study EPS was clearly superior to Holter monitoring for evaluating amiodarone efficacy, but EPS is invasive and is not always performed in all patients.

Amiodarone, ICD and LVEF

Zhu et al suggested that EPS testing during amiodarone therapy was useful for predicting arrhythmia recurrence in patients without new or worsening congestive heart failure[7] Other previous reports suggest that patients with lower LVEF (<35%) have a higher incidence of sudden cardiac death after amiodarone[16–18] Those results are consisted with our subgroup analysis showing that EPS-guided amiodarone therapy is beneficial for patients with LVEF ≥30% but not <30%. Therefore, it is suggested that ICD is indicated in patients with lower LVEF (≤30–35%) and a history of syncope or sustained VT/VF[17,24,25] On the other hand, patients with a relatively preserved LVEF (≥35%) do not always have better survival by ICD compared with amiodarone[16]

In this study, EPS-guided amiodarone responders with a LVEF ≥30% were considered to be lower risk for sudden cardiac death, whereas patients judged as amiodarone non-responders or with LVEF <30% remain high risk for sudden death. Although our data could not compare between amiodarone and ICD therapy in high-risk patients, amiodarone-treated patients with lower LVEF, but not an implanted ICD, remain at higher risk of sudden death (Fig 4B) and should be considered for additional ICD therapy, as previously reported[24]

In patients with congestive heart failure and LVEF <35%, a recent randomized study reported that amiodarone has no favorable effect on survival compared with placebo, but that ICD therapy reduced overall mortality by 23%[19] Although ICD reduces mortality compared with antiarrhythmic drugs, it is estimated that up to 50% of patients with an ICD ultimately need antiarrhythmic drug therapy to suppress frequent episodes of VT or supraventricular tachyarrhythmias, and that amiodarone is the most commonly used drug for this purpose in Japanese patients[15] Recently, Connolly et al reported that amiodarone plus β-blocker was effective for preventing ICD shocks, but increased the risk of drug-related adverse effect[26] Therefore, further studies in the Japanese patient population are necessary to evaluate whether or not amiodarone can improve a patient's clinical outcome by reducing the amount of ICD shocks![14]

Study Limitations

First, the study was not a prospective evaluation of EPS- or Holter-guided amiodarone treatment, so the direct efficacy of EPS or Holter-guided amiodarone in preventing the recurrence of VT/VF was not demonstrated; rather, an excellent prognosis for patients treated with EPS-guided amiodarone, especially in patients with a well-preserved LVEF, was demonstrated. Second, this study compared follow-up results between patients judged as amiodarone responder or non-responder by EPS, but did not compare

amiodarone responders with control patients. Therefore, it might overestimate the effectiveness of EPS-guided amiodarone therapy for suppression of recurrent VT/VF. Third, this study contained a small number of patients, and a multicenter trial with a large number of patients will be necessary to demonstrate the effect of amiodarone and ICD therapy more accurately in Japanese patients![14,15] Fourth, this study focused on the risk of recurrent (secondary) VT/VF, not on primary prevention. It is still controversial whether amiodarone and/or ICD are indicated in patients with nonsustained VT and lower LVEF for primary prevention of sudden death.

References

1. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. *Circulation* 1997; **96:** 2823–2829.
2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999; **100:** 2025–2034.
3. Investigators ATM-A. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: Meta-analysis of individual data from 6500 patients in randomised trials. *Lancet* 1997; **350:** 1417–1424.
4. Aiba T, Kurita T, Taguchi A, Shimizu W, Suyama K, Aihara N, et al. Long-term efficacy of empirical chronic amiodarone therapy in patients with sustained ventricular tachyarrhythmia and structural heart disease. *Circ J* 2002; **66:** 367–371.
5. Kadish AH, Buxton AE, Waxman HL, Flores B, Josephson ME, Marchlinski FE. Usefulness of electrophysiologic study to determine the clinical tolerance of arrhythmia recurrences during amiodarone therapy. *J Am Coll Cardiol* 1987; **10:** 90–96.
6. Veltri EP, Reid PR, Platia EV, Griffith LS. Amiodarone in the treatment of life-threatening ventricular tachycardia: Role of Holter monitoring in predicting long-term clinical efficacy. *J Am Coll Cardiol* 1985; **6:** 806–813.
7. Zhu J, Haines DE, Lerman BB, DiMarco JP. Predictors of efficacy of amiodarone and characteristics of recurrence of arrhythmia in patients with sustained ventricular tachycardia and coronary artery disease. *Circulation* 1987; **76:** 802–809.
8. Greenspon AJ, Volosin KJ, Greenberg RM, Jefferies L, Rotmensch HH. Amiodarone therapy: Role of early and late electrophysiologic studies. *J Am Coll Cardiol* 1988; **11:** 117–123.
9. Yuge M, Niwano S, Moriguchi M, Sasaki T, Hirasawa S, Imaki R, et al. Clinical significance of the electrophysiologic study (EPS)-guided therapy for the secondary prevention of ventricular tachycardia. *Circ J* 2006; **70:** 268–272.
10. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease: Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; **341:** 1882–1890.
11. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; **101:** 1297–1302.
12. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; **102:** 748–754.
13. Schlapfer J, Rapp F, Kappenberger L, Fromer M. Electrophysiologically guided amiodarone therapy versus the implantable cardioverter-defibrillator for sustained ventricular tachyarrhythmias after myocardial infarction: Results of long-term follow-up. *J Am Coll Cardiol* 2002; **39:** 1813–1819.
14. Kurita T, Mitamura H, Aizawa Y, Nitta T, Aonuma K, Tsuboi N, et al. Japanese randomized trial for investigation of a combined therapy of amiodarone and implantable cardioverter defibrillator in patients with ventricular tachycardia and fibrillation: The Nippon ICD Plus Pharmacologic Option Necessity study design. *Circ J* 2006; **70:** 316–320.
15. Satomi K, Kurita T, Takatsuki S, Yokoyama Y, Chinushi M, Tsuboi N, et al. Amiodarone therapy in patients implanted with cardioverter-defibrillator for life-threatening ventricular arrhythmias. *Circ J* 2006; **70:** 977–984.
16. Domanski MJ, Sakseena S, Epstein AE, Hallstrom AP, Brodsky MA, Kim S, et al. Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias: AVID Investigators: Antiarrhythmics Versus Implantable Defibrillators. *J Am Coll Cardiol* 1999; **34:** 1090–1095.
17. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials: AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study; Cardiac Arrest Study Hamburg; Canadian Implantable Defibrillator Study. *Eur Heart J* 2000; **21:** 2071–2078.
18. Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: The Canadian Implantable Defibrillator Study. *Circulation* 2000; **101:** 1660–1664.
19. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–237.
20. Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias: Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. *N Engl J Med* 1993; **329:** 452–458.
21. Horowitz LN, Greenspan AM, Spielman SR, Webb CR, Morganroth J, Rotmensch H, et al. Usefulness of electrophysiologic testing in evaluation of amiodarone therapy for sustained ventricular tachyarrhythmias associated with coronary heart disease. *Am J Cardiol* 1985; **55:** 367–371.
22. McGovern B, Garan H, Malacoff RF, DiMarco JP, Grant G, Sellers TD, et al. Long-term clinical outcome of ventricular tachycardia or fibrillation treated with amiodarone. *Am J Cardiol* 1984; **53:** 1558–1563.
23. Nasir N Jr, Doyle TK, Wheeler SH, Pacifico A. Usefulness of Holter monitoring in predicting efficacy of amiodarone therapy for sustained ventricular tachycardia associated with coronary artery disease. *Am J Cardiol* 1994; **73:** 554–558.
24. Olson PJ, Woelfel A, Simpson RJ Jr, Foster JR. Stratification of sudden death risk in patients receiving long-term amiodarone treatment for sustained ventricular tachycardia or ventricular fibrillation. *Am J Cardiol* 1993; **71:** 823–826.
25. Grimm W, Hoffmann J, Menz V, Luck K, Maisch B. Programmed ventricular stimulation for arrhythmia risk prediction in patients with idiopathic dilated cardiomyopathy and nonsustained ventricular tachycardia. *J Am Coll Cardiol* 1998; **32:** 739–745.
26. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: The OPTIC Study: A randomized trial. *JAMA* 2006; **295:** 165–171.

Journal of Human Hypertension (2007) 21, 212–219

www.nature.com/jhh

ORIGINAL ARTICLE

Reverse white-coat effect as an independent risk for left ventricular concentric hypertrophy in patients with treated essential hypertension

M Tomiyama, T Horio, K Kamide, S Nakamura, F Yoshihara, H Nakata, H Nakahama and Y Kawano

Division of Hypertension and Nephrology, Department of Medicine, National Cardiovascular Center, Suita, Japan

Recent studies have shown that the converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension' is associated with poor cardiovascular prognosis. We assessed the hypothesis that this phenomenon may specifically influence left ventricular (LV) structure in treated hypertensive patients. A total of 272 outpatients (mean age, 65 years) with chronically treated essential hypertension and without remarkable white-coat effect were enrolled. Patients were classified into two groups according to office and daytime ambulatory systolic blood pressure (SBP); that is subjects without (Group 1: office SBP $\geqslant$ daytime SBP, $n=149$) and with reverse white-coat effect (Group 2: office SBP < daytime SBP, $n=123$). LV mass index and relative wall thickness were echocardiographically determined. In all subjects, LV mass index and relative wall thickness were positively correlated with daytime and 24-h SBP, but not with office SBP. In addition, these two indices were inversely correlated with office – daytime SBP difference. LV mass index (136 ± 31 and $115\pm28\,g/m^2$, mean $\pm$ s.d.) and relative wall thickness (0.49 ± 0.09 and 0.46 ± 0.07) were significantly greater in Group 2 than in Group 1. As for LV geometric patterns, Group 2 had a significantly higher rate of concentric hypertrophy compared with Group 1 (48 and 28%). Multivariate analyses revealed that the presence of reverse white-coat effect was a predictor for LV concentric hypertrophy, independent of age, sex, hypertension duration, antihypertensive treatment and ambulatory blood pressure levels. Our findings demonstrate that reverse white-coat effect is an independent risk factor for LV hypertrophy, especially concentric hypertrophy, in treated hypertensive patients.

Journal of Human Hypertension (2007) **21**, 212–219.
doi:10.1038/sj.jhh.1002127; published online 14 December 2006

Keywords: blood pressure; ambulatory; cardiac hypertrophy; geometry

Introduction

Ambulatory blood pressure (BP) is an important determinant of target organ damage and a significant predictor for cardiovascular morbidity and mortality in hypertensive patients.[1–6] There is often a discrepancy between office and ambulatory BPs, such as white-coat hypertension, a normal ambulatory but elevated office BP. On the other hand, the converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension', that is, a high ambulatory but normal (or well-controlled) office BP, has received little attention.[7] Whereas, some studies have revealed that the proportion of subjects with reverse white-coat condition reaches 20–40% of the general population and hypertensives.[8,9] In treated hypertensive patients with this phenomenon, particularly, the chance of active and sufficient antihypertensive treatment may be lost by an apparent well-controlled BP in the office. Recent studies suggested that an elevated ambulatory or home BP despite a well-controlled office BP is associated with poor cardiovascular prognosis in treated hypertensive patients.[10,11] However, it remains unclear what mechanism is involved in the association of reverse white-coat phenomenon with cardiovascular prognosis.

Left ventricular hypertrophy (LVH), which is a common cardiac consequence of hypertension, is well known to be an independent risk factor for cardiovascular complications and death.[12,13] In addition, left ventricular (LV) morphologic

Correspondence: Dr T Horio, Division of Hypertension and Nephrology, Department of Medicine, National Cardiovascular Center, 5-7-1, Fujishirodai, Suita, Osaka 565-8565, Japan.
E-mail: thorio@ri.ncvc.go.jp
Received 4 August 2006; revised 23 October 2006; accepted 30 October 2006; published online 14 December 2006

The geometry of LV was stratified into four different patterns according to the values of LVMI (< or ⩾125/110 g/m^2, men/women) and RWT (< or ⩾0.44). Patients with increased LVMI and increased RWT were considered to have concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have eccentric hypertrophy. Those with normal LVMI and increased or normal RWT were considered to have concentric remodelling or normal geometry, respectively.

Biochemical measurement

Blood samples were obtained in the morning after an overnight fast. Total cholesterol, triglycerides, fasting plasma glucose, haemoglobin A1c and serum creatinine levels were determined by standard laboratory measurements. Creatinine clearance was calculated from the Cockcroft-Gault formula.[22]

Statistical analysis

Statistical analysis was performed using StatView Version 5 Software (Abacus Concepts Inc., Berkeley, CA, USA). Values are expressed as the mean ± s.d. Simple correlations between variables were assessed using univariate linear regression analyses and Pearson's correlation coefficient. An unpaired Student's *t*-test was used for comparison between the two groups. The significance of differences among the three groups was evaluated by an unpaired ANOVA with subsequent Fisher's multiple comparison test. A multiple logistic regression analysis was performed to identify independent determinants of LV mass increase and concentric hypertrophy. A value of $P<0.05$ was accepted as statistically significant.

Results

Simple correlations of office and ambulatory BP levels with two indices of LV structural changes, LVMI and RWT, in all subjects are shown in Table 1. Office systolic or diastolic BP had no correlation with either LVMI or RWT. In contrast, LVMI and RWT were positively correlated with daytime and 24-h systolic BPs, and LVMI was also correlated with night time systolic BP. In addition, these two indices were significantly correlated with the difference between office BP and daytime BP. As shown in Figure 1, LVMI had a close negative correlation with office–daytime systolic BP difference ($r=-0.377$, $P<0.001$). RWT were also inversely correlated with office–daytime systolic BP difference ($r=-0.170$, $P=0.005$). These results suggested that reverse white-coat effect was significantly associated with increases in LVMI and RWT.

Clinical characteristics of the two subject groups classified according to the difference between office and daytime ambulatory systolic BP levels are summarized in Table 2. One hundred and twenty-three (45%) patients were identified as having reverse white-coat effect (Group 2), and the other 149 (55%) patients belonged to Group 1. The proportion of men and the rate of habitual drinkers

Table 1 Correlation of office and ambulatory blood pressure with left ventricular structure in all subjects

	LVMI		*RWT*	
	r	P	r	P
Office systolic BP	0.039	0.526	0.014	0.816
Office diastolic BP	−0.124	0.053	−0.040	0.508
Daytime systolic BP	0.290	<0.001	0.173	0.004
Daytime diastolic BP	0.020	0.742	0.100	0.099
Night time systolic BP	0.318	<0.001	0.113	0.062
Night time diastolic BP	0.099	0.104	0.078	0.198
24-h systolic BP	0.325	<0.001	0.158	0.009
24-h diastolic BP	0.051	0.398	0.096	0.113
(Office – daytime) systolic BP	−0.377	<0.001	−0.170	0.005
(Office – daytime) diastolic BP	−0.211	<0.001	−0.147	0.015

Abbreviations: BP, blood pressure; LVMI, left ventricular mass index; RWT, relative wall thickness.

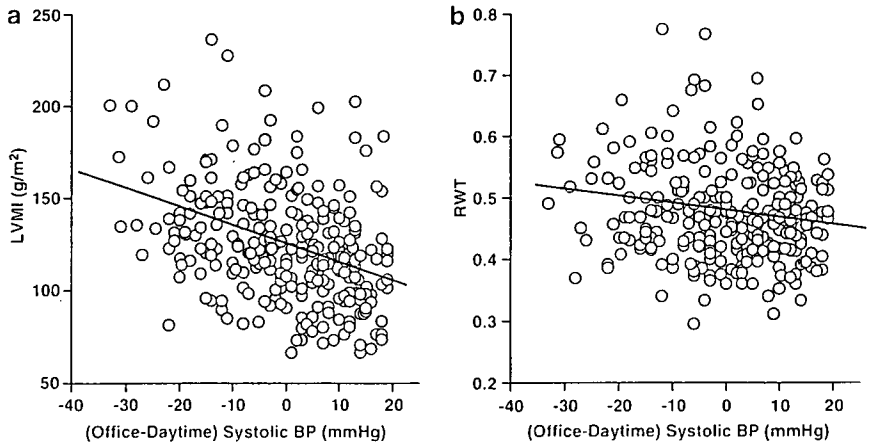

Figure 1 Correlation of the difference between office and daytime systolic BP levels with LVMI (a, $r=-0.377$, $P<0.001$) and RWT (b, $r=-0.170$, $P=0.005$) in all subjects.

Table 2 Clinical characteristics of two study groups

	Group 1 (n = 149)	*Group 2 (n = 123)*	P
Age (years)	65.8 ± 9.1	65.1 ± 11.0	0.593
Sex (male) (%)	41.6	65.0	<0.001
Body mass index (kg/m²)	24.2 ± 2.9	24.7 ± 4.0	0.182
Duration of hypertension (years)	17.6 ± 10.8	17.8 ± 11.0	0.850
Diabetes mellitus (%)	19.5	23.6	0.412
Hyperlipidemia (%)	64.9	66.1	0.831
Current smoking (%)	15.6	21.1	0.235
Habitual drinking (%)	50.7	63.6	0.033
Creatinine clearance (ml/min)	81.5 ± 24.8	85.1 ± 32.8	0.297
Fasting plasma glucose (mmol/l)	5.7 ± 1.2	5.8 ± 1.1	0.486
Hemoglobin A1c (%)	5.6 ± 0.8	5.7 ± 0.7	0.257
Total cholesterol (mmol/l)	5.3 ± 0.8	5.2 ± 0.7	0.576
Triglycerides (mmol/l)	1.4 ± 0.7	1.5 ± 0.8	0.126
Antihypertensive treatment			
Period of medication (years)	12.4 ± 9.3	11.7 ± 9.1	0.497
Ca channel blockers (%)	71.8	71.5	0.961
RAS inhibitors (%)	49.7	53.7	0.514
β-Blockers (%)	28.2	32.5	0.440
Diuretics (%)	16.8	22.8	0.216
Others (%)	9.4	12.2	0.458
Total number of classes	1.8 ± 0.9	1.9 ± 0.9	0.141
Office systolic BP (mm Hg)	145.6 ± 12.7	133.8 ± 11.6	<0.001
Office diastolic BP (mm Hg)	83.4 ± 9.9	78.8 ± 10.0	<0.001
Daytime systolic BP (mm Hg)	136.5 ± 12.6	145.1 ± 11.9	<0.001
Daytime diastolic BP (mm Hg)	80.1 ± 9.3	84.8 ± 11.5	<0.001
Night time systolic BP (mm Hg)	126.8 ± 14.9	134.1 ± 15.8	<0.001
Night time diastolic BP (mm Hg)	73.1 ± 9.5	76.9 ± 11.1	0.002
24-h systolic BP (mm Hg)	134.0 ± 12.3	141.6 ± 12.2	<0.001
24-h diastolic BP (mm Hg)	78.2 ± 9.0	82.3 ± 10.5	<0.001
Nocturnal systolic BP dipping (%)	7.1 ± 8.0	7.6 ± 8.0	0.572
Nocturnal diastolic BP dipping (%)	8.5 ± 8.4	9.0 ± 8.5	0.671

Abbreviations: BP, blood pressure; RAS, renin angiotensin system.
RAS inhibitors represent angiotensin II receptor blockers and angiotensin converting enzyme inhibitors. Values are mean ± s.d. or percentage.

were significantly higher in Group 2 than in Group 1. Age, body mass index, hypertension duration, the prevalence of diabetes mellitus and hyperlipidemia, the rate of current smokers, renal function and glucose and lipid parameters did not differ between the two groups. In addition, there were no intergroup differences in the period of medication, the use of any class of antihypertensive agent and the total number of classes of antihypertensive drugs.

Office and ambulatory BP levels had clear differences between the two groups. That is, Group 2 had significantly lower office systolic and diastolic BPs than Group 1, but daytime, night time, and average 24-h ambulatory BPs in Group 2 were significantly elevated compared with those in Group 1. The degree of nocturnal BP dipping, an index of circadian BP variation, did not differ between the two groups.

The comparison of echocardiographic parameters between the two groups is shown in Table 3. Group 2 had a significantly greater LVMI than Group 1, resulting from more increased LV wall thickness and internal dimension. RWT was also significantly increased in Group 2 compared with Group 1. In addition, the prevalence of LVH, defined as an increased LVMI by sex, was significantly higher in Group 2. There was no difference in fractional shortening between the two groups.

Table 3 Comparison of ecchocardiographic parameters between the two groups

	Group 1 (n = 149)	*Group 2 (n = 123)*	P
IVSTd (mm)	10.3 ± 1.5	11.4 ± 1.9	<0.001
PWTd (mm)	10.3 ± 1.4	11.1 ± 1.5	<0.001
LVDd (mm)	44.8 ± 4.5	46.8 ± 4.2	<0.001
LVDs (mm)	26.5 ± 4.9	27.7 ± 4.6	0.037
Fractional shortening (%)	41.1 ± 7.4	41.0 ± 6.8	0.920
LVMI (g/m²)	115.3 ± 28.3	136.4 ± 30.8	<0.001
RWT	0.46 ± 0.07	0.49 ± 0.09	0.010
Prevalence of LVH (%)	41.6	65.9	<0.001

Abbreviations: IVSTd, interventricular septal thickness at end-diastole; LVDd, left ventricular diameter at end-diastole; LVDs, left ventricular diameter at end-systole; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; PWTd, posterior wall thickness at end-diastole; RWT, relative wall thickness.
LVH is defined as LVMI of ⩾125 g/m² in men and 110 g/m² in women. Values are mean ± s.d. or percentage.

To assess the impact of reverse white-coat effect on LVH, Group 2 was divided into two sub-groups by the extent of its phenomenon. As shown in Figure 2, both LVMI and prevalence of LVH were

Table 2 Clinical characteristics of two study groups

	Group 1 (n = 149)	*Group 2 (n = 123)*	P
Age (years)	65.8 ± 9.1	65.1 ± 11.0	0.593
Sex (male) (%)	41.6	65.0	<0.001
Body mass index (kg/m²)	24.2 ± 2.9	24.7 ± 4.0	0.182
Duration of hypertension (years)	17.6 ± 10.8	17.8 ± 11.0	0.850
Diabetes mellitus (%)	19.5	23.6	0.412
Hyperlipidemia (%)	64.9	66.1	0.831
Current smoking (%)	15.6	21.1	0.235
Habitual drinking (%)	50.7	63.6	0.033
Creatinine clearance (ml/min)	81.5 ± 24.8	85.1 ± 32.8	0.297
Fasting plasma glucose (mmol/l)	5.7 ± 1.2	5.8 ± 1.1	0.486
Hemoglobin A1c (%)	5.6 ± 0.8	5.7 ± 0.7	0.257
Total cholesterol (mmol/l)	5.3 ± 0.8	5.2 ± 0.7	0.576
Triglycerides (mmol/l)	1.4 ± 0.7	1.5 ± 0.8	0.126
Antihypertensive treatment			
Period of medication (years)	12.4 ± 9.3	11.7 ± 9.1	0.497
Ca channel blockers (%)	71.8	71.5	0.961
RAS inhibitors (%)	49.7	53.7	0.514
β-Blockers (%)	28.2	32.5	0.440
Diuretics (%)	16.8	22.8	0.216
Others (%)	9.4	12.2	0.458
Total number of classes	1.8 ± 0.9	1.9 ± 0.9	0.141
Office systolic BP (mm Hg)	145.6 ± 12.7	133.8 ± 11.6	<0.001
Office diastolic BP (mm Hg)	83.4 ± 9.9	78.8 ± 10.0	<0.001
Daytime systolic BP (mm Hg)	136.5 ± 12.6	145.1 ± 11.9	<0.001
Daytime diastolic BP (mm Hg)	80.1 ± 9.3	84.8 ± 11.5	<0.001
Night time systolic BP (mm Hg)	126.8 ± 14.9	134.1 ± 15.8	<0.001
Night time diastolic BP (mm Hg)	73.1 ± 9.5	76.9 ± 11.1	0.002
24-h systolic BP (mm Hg)	134.0 ± 12.3	141.6 ± 12.2	<0.001
24-h diastolic BP (mm Hg)	78.2 ± 9.0	82.3 ± 10.5	<0.001
Nocturnal systolic BP dipping (%)	7.1 ± 8.0	7.6 ± 8.0	0.572
Nocturnal diastolic BP dipping (%)	8.5 ± 8.4	9.0 ± 8.5	0.671

Abbreviations: BP, blood pressure; RAS, renin angiotensin system.
RAS inhibitors represent angiotensin II receptor blockers and angiotensin converting enzyme inhibitors. Values are mean ± s.d. or percentage.

were significantly higher in Group 2 than in Group 1. Age, body mass index, hypertension duration, the prevalence of diabetes mellitus and hyperlipidemia, the rate of current smokers, renal function and glucose and lipid parameters did not differ between the two groups. In addition, there were no inter-group differences in the period of medication, the use of any class of antihypertensive agent and the total number of classes of antihypertensive drugs.

Office and ambulatory BP levels had clear differences between the two groups. That is, Group 2 had significantly lower office systolic and diastolic BPs than Group 1, but daytime, night time, and average 24-h ambulatory BPs in Group 2 were significantly elevated compared with those in Group 1. The degree of nocturnal BP dipping, an index of circadian BP variation, did not differ between the two groups.

The comparison of echocardiographic parameters between the two groups is shown in Table 3. Group 2 had a significantly greater LVMI than Group 1, resulting from more increased LV wall thickness and internal dimension. RWT was also significantly increased in Group 2 compared with Group 1. In addition, the prevalence of LVH, defined as an increased LVMI by sex, was significantly higher in Group 2. There was no difference in fractional shortening between the two groups.

Table 3 Comparison of ecchocardiographic parameters between the two groups

	Group 1 (n = 149)	*Group 2 (n = 123)*	P
IVSTd (mm)	10.3 ± 1.5	11.4 ± 1.9	<0.001
PWTd (mm)	10.3 ± 1.4	11.1 ± 1.5	<0.001
LVDd (mm)	44.8 ± 4.5	46.8 ± 4.2	<0.001
LVDs (mm)	26.5 ± 4.9	27.7 ± 4.6	0.037
Fractional shortening (%)	41.1 ± 7.4	41.0 ± 6.8	0.920
LVMI (g/m²)	115.3 ± 28.3	136.4 ± 30.8	<0.001
RWT	0.46 ± 0.07	0.49 ± 0.09	0.010
Prevalence of LVH (%)	41.6	65.9	<0.001

Abbreviations: IVSTd, interventricular septal thickness at end-diastole; LVDd, left ventricular diameter at end-diastole; LVDs, left ventricular diameter at end-systole; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; PWTd, posterior wall thickness at end-diastole; RWT, relative wall thickness.
LVH is defined as LVMI of ⩾ 125 g/m² in men and 110 g/m² in women. Values are mean ± s.d. or percentage.

To assess the impact of reverse white-coat effect on LVH, Group 2 was divided into two sub-groups by the extent of its phenomenon. As shown in Figure 2, both LVMI and prevalence of LVH were

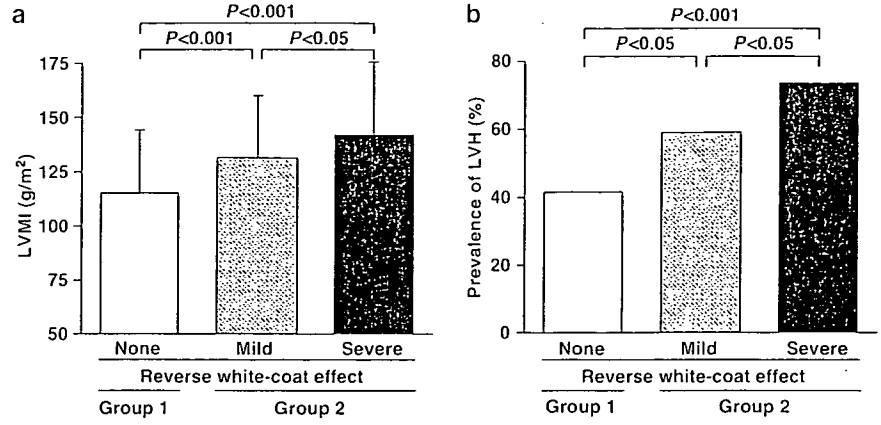

Figure 2 Comparison of LVMI (a) and prevalence of LVH (b) among the three groups classified by the extent of reverse white-coat effect. None, office systolic BP ≥ daytime systolic BP (i.e., Group 1, $n=149$); Mild, office systolic BP < daytime systolic BP, but daytime systolic BP−office systolic BP < 10 mm Hg ($n=63$); Severe, daytime systolic BP−office systolic BP ≥ 10 mm Hg ($n=60$). LVH is defined as LVMI of ≥125 g/m² in men and 110 g/m² in women. Values are given as the mean ± s.d. (a) or percentage (b).

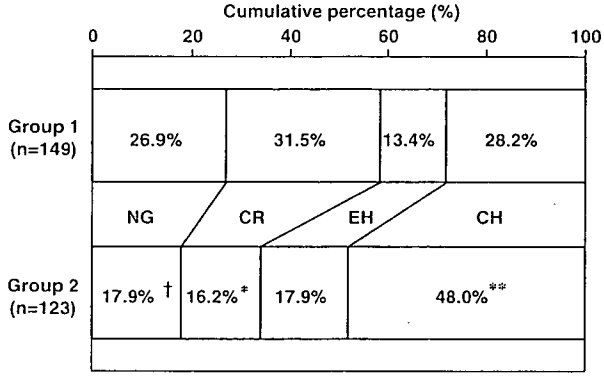

Figure 3 Comparison of LV geometric patterns between the two groups. NG, normal geometry (normal LVMI and RWT); CR, concentric remodelling (normal LVMI and increased RWT); EH, eccentric hypertrophy (increased LVMI and normal RWT); CH, concentric hypertrophy (increased LVMI and RWT). †$P<0.05$, *$P<0.01$, and **$P<0.001$ vs Group 1.

significantly greater in subjects with mild reverse white-coat effect (office systolic BP < daytime systolic BP, but daytime systolic BP−office systolic BP < 10 mm Hg) than in those without reverse white-coat effect (i.e., Group 1), and these values were further increased significantly in the sub-group with severe reverse white-coat effect (daytime systolic BP−office systolic BP ≥ 10 mm Hg).

Figure 3 shows the comparison of LV geometric patterns between the two groups. Group 2 had a significantly higher rate of concentric hypertrophy compared with Group 1 (48 vs 28%, $P<0.001$). In contrast, the rates of patients with normal geometry and concentric remodelling were significantly lower in Group 2 than in Group 1.

To confirm whether the influence of reverse white-coat phenomenon on LV mass increase and specific geometric change was independent of various clinical parameters, we investigated possible predictive factors using a multiple logistic regression analysis in all subjects (Table 4). Although average 24-h systolic BP was the strongest predictor for both LVH and concentric hypertrophy, the presence of reverse white-coat effect (i.e., Group 2) was found to be a significant determinant for these LV structural changes, independent of age, sex, body mass index, hypertension duration, the use of any class of antihypertensive agent and 24-h systolic and diastolic BP levels (for LVH: odds ratio 2.42 vs Group 1, $P=0.005$; for concentric hypertrophy: odds ratio 1.89, $P=0.039$). The significant predictive value of reverse white-coat effect remained even when daytime systolic and diastolic BPs, instead of 24-h BPs, were adopted as independent predictors (data not shown).

Discussion

This study has demonstrated that the presence of reverse white-coat effect is one of the independent predictors for LVH, especially for LV concentric hypertrophy, in patients with treated essential hypertension. The new findings suggest that reverse white-coat phenomenon, independent of average ambulatory blood pressure levels, may have an unfavourable influence on left ventricular geometry in essential hypertension.

The present subjects with reverse white-coat effect (Group 2) had a controlled office BP in spite of elevated ambulatory BP, indicating that the group took on an aspect of masked hypertension. There have been a few studies reporting the possible association between masked hypertension and cardiac and carotid arterial structural changes in the general population. Liu *et al.*[23] found that LV mass and carotid wall thickness in patients with masked hypertension were significantly greater than those in true normotensive subjects and similar to those in patients with sustained hypertension. The data from the PAMELA Study also showed that LVMI was

Table 4 Independent predictors for left ventricular mass increase and concentric hypertrophy by multiple logistic regression analysis

	LVH		*Concentric hypertrophy*	
	OR (95% CI)	P	*OR (95% CI)*	P
Age (10 years)	0.88 (0.58–1.34)	0.544	0.70 (0.46–1.05)	0.087
Sex (male)	0.60 (0.30–1.16)	0.128	0.82 (0.42–1.60)	0.557
Body mass index (1 kg/m²)	1.10 (1.00–1.23)	0.046	1.10 (1.00–1.22)	0.053
Hypertension duration (1 year)	1.02 (0.99–1.05)	0.123	1.03 (1.00–1.06)	0.028
Diabetes mellitus (yes)	1.04 (0.48–2.22)	0.929	1.02 (0.49–2.13)	0.959
Hyperlipidemia (yes)	1.49 (0.82–2.71)	0.186	1.35 (0.73–2.47)	0.339
Current smoking (yes)	0.99 (0.46–2.13)	0.978	1.25 (0.60–2.58)	0.553
Habitual drinking (yes)	1.09 (0.58–2.06)	0.783	1.22 (0.64–2.32)	0.541
Creatinine clearance (10 ml/min)	0.91 (0.77–1.06)	0.231	0.87 (0.74–1.02)	0.095
Ca channel blocker (yes)	1.36 (0.67–2.77)	0.402	1.09 (0.53–2.24)	0.808
RAS inhibitor (yes)	1.15 (0.60–2.21)	0.678	1.57 (0.82–2.99)	0.170
β-Blocker (yes)	1.89 (0.99–3.59)	0.052	1.36 (0.73–2.55)	0.337
Diuretic (yes)	1.04 (0.49–2.22)	0.921	0.72 (0.34–1.56)	0.407
24-h systolic BP (10 mm Hg)	2.35 (1.66–3.33)	<0.001	1.97 (1.45–2.68)	<0.001
24-h diastolic BP (10 mm Hg)	0.60 (0.40–0.90)	0.014	0.67 (0.45–0.98)	0.041
Reverse white-coat effect				
Absence (Group 1)	1 (reference)		1 (reference)	
Presence (Group 2)	2.42 (1.31–4.48)	0.005	1.89 (1.03–3.44)	0.039

Abbreviations: BP, blood pressure; CI, confidence interval; LVH, left ventricular hypertrophy; OR, odds ratio; RAS, renin angiotensin system. RAS inhibitor represents angiotensin II receptor blocker or angiotensin converting enzyme inhibitor. LVH is defined as LVMI of ⩾125 g/m² in men and 110 g/m² in women. Concentric hypertrophy is defined as LVH combined with increased RWT (⩾0.44).

increased in untreated subjects with masked hypertension and sustained hypertension than in those with true normotension.[24] In addition, our recent study showed that masked hypertension was associated with advanced target organ damage in treated hypertensive patients, comparable to that in cases of sustained hypertension.[25] Furthermore, prospective studies have revealed that a high ambulatory or home BP is a powerful predictor for cardiovascular morbidity and mortality in the general population and treated hypertensive patients even when their office BP is normal or well controlled.[10,11,26–28] As for the association between LV geometry and cardiovascular prognosis, it was reported that hypertensive patients with concentric hypertrophy among four LV geometric patterns had the highest incidence of cardiovascular events and death.[13] Taken together, it is likely that advanced target organ changes including LV concentric hypertrophy in patients with masked hypertension or reverse white-coat condition are linked to poor cardiovascular prognosis in such patients.

A higher level of ambulatory BP is a major determinant of target organ damage in hypertensive patients.[1,2] In the present study, however, the presence of reverse white-coat effect was a significant predictor for LVH and concentric hypertrophy, independent of average 24-h ambulatory BP levels. Other factors than a higher ambulatory BP could contribute to target organ damage in reverse white-coat hypertension. Our study has not provided the specific mechanism by which reverse white-coat effect could promote LV concentric hypertrophy in patients with treated hypertension. Therefore, further investigations are required to clarify how reverse white-coat or masked hypertension has a specific unfavourable effect on the hypertensive target organ.

There were some limitations in our study. The present findings were derived from cross-sectional data on the basis of one-time examination of ambulatory BP monitoring and echocardiography. Our subjects were divided into subgroups based on office–daytime difference only in systolic BP, not considering diastolic BP difference. In addition, cardiac magnetic resonance imaging might be more adequate than echocardiography in evaluating LV mass exactly.

All patients in the present study had received antihypertensive medication. As another limitation of this study, therefore, we must consider the possibility that different classes of antihypertensive drugs may have differently affected the development of LVH, partly independently of their BP-lowering effects. Renin angiotensin system inhibitors, particularly, are known to have BP fall-independent protective effects on hypertensive target organ. However, the percentage of patients treated with angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors did not differ between the two study groups. Our multivariate analysis also showed that the association of reverse white-coat effect with LVH and concentric hypertrophy was independent of the use of any class of antihypertensive agent.

In conclusion, the present study indicates that reverse white-coat effect is a significant determinant of LVH, especially concentric hypertrophy, in patients with treated essential hypertension, independent of average ambulatory BP levels and

various other clinical risk factors. Our findings suggest that the presence of this phenomenon may be an independent risk for the adverse LV geometric change in treated hypertensive patients and ambulatory BP monitoring seems to be necessary to unmask this latent risk that is not detectable by routine BP measuring in the office.

What is known about this topic

- Ambulatory blood pressure is an important determinant of target organ damage and a predictor for cardiovascular morbidity and mortality in hypertensive patients.
- The converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension' is associated with poor cardiovascular prognosis.
- Left ventricular hypertrophy, especially concentric hypertrophy, is a significant risk factor for cardiovascular complications and death.

What this study adds

- Reverse white-coat effect was an independent predictor for left ventricular hypertrophy, especially for concentric hypertrophy, in treated hypertensive patients.
- The presence of reverse white-coat phenomenon, independent of average ambulatory blood pressure levels, may have an unfavourable influence on left ventricular geometry.

Acknowledgements

This study was supported by the Grant for Cardiovascular Disease (11C-5) and the Health and Labor Sciences Research Grants (H14-kouka-021) from the Ministry of Health, Labor and Welfare of Japan, and the Grant from Japan Cardiovascular Research Foundation. We thank Chikako Tokudome, Yoko Oikawa, Yoko Saito, and Miho Nishibata for their secretarial assistance.

References

1 Pickering TG, Harshfield GA, Devereux RB, Laragh JH. What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension* 1985; 7: 171–177.
2 Schillaci G, Verdecchia P, Sacchi N, Bruni B, Benemio G, Pede S *et al.* Clinical relevance of office underestimation of usual blood pressure in treated hypertension. *Am J Hypertens* 2000; 13: 523–528.
3 Cuspidi C, Meani S, Fusi V, Valerio C, Catini E, Magrini F *et al.* Isolated ambulatory hypertension and changes in target organ damage in treated hypertensive patients. *J Hum Hypertens* 2005; 19: 471–477.
4 Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA* 1983; 249: 2792–2798.
5 Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW *et al.* Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; 282: 539–546.
6 Verdecchia P, Reboldi G, Porcellati C, Schillaci G, Pede S, Bentivoglio M *et al.* Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *J Am Coll Cardiol* 2002; 39: 878–885.
7 Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002; 40: 795–796.
8 Wing LMH, Brown MA, Beilin LJ, Ryan P, Reid CM. 'Reverse white-coat hypertension' in older hypertensives. *J Hypertens* 2002; 20: 639–644.
9 Bombelli M, Sega R, Facchetti R, Corrao G, Friz HP, Vertemati AM *et al.* Prevalence and clinical significance of a greater ambulatory versus office blood pressure ('reversed white coat' condition) in a general population. *J Hypertens* 2005; 23: 513–520.
10 Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH *et al.* Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; 348: 2407–2415.
11 Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B *et al.* Cardiovascular prognosis of 'masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; 291: 1342–1349.
12 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; 322: 1561–1566.
13 Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114: 345–352.
14 Hata Y, Mabuchi H, Saito Y, Itakura H, Egusa G, Ito H *et al.* Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. *J Atheroscler Thromb* 2002; 9: 1–27.
15 Kawano Y, Matsuoka H, Takishita S, Omae T. Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension* 1998; 32: 260–265.
16 Imai Y, Sasaki S, Minami N, Munakata M, Hashimito T, Sakuma H *et al.* The accuracy and performance of the A&D TM 2421, a new ambulatory blood pressure monitoring device based on the cuff-oscillometric and the Korotkoff sound technique. *Am J Hypertens* 1992; 5: 719–726.
17 Horio T, Miyazato J, Kamide K, Takiuchi S, Kawano Y. Influence of low high-density lipoprotein cholesterol on left ventricular hypertrophand diastolic function in essential hypertension. *Am J Hypertens* 2003; 16: 938–944.
18 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072–1083.
19 Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; 2: 358–367.
20 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 1977; 55: 613–618.

21 Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W *et al*. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hypertens* 2003; **21**: 1779–1786.
22 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
23 Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med* 1999; **131**: 564–572.
24 Sega R, Trocino G, Lanzarotti A, Carugo S, Cesana G, Schiavina R *et al*. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). *Circulation* 2001; **104**: 1385–1392.
25 Tomiyama M, Horio T, Yoshii M, Takiuchi S, Kamide K, Nakamura S *et al*. Masked hypertension and target organ damage in treated hypertensive patients. *Am J Hypertens* 2006; **19**: 880–886.
26 Björklund K, Lind L, Zethelius B, Andrén B, Lithell H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation* 2003; **107**: 1297–1302.
27 Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J *et al*. Prognosis of 'masked' hypertension and 'white-coat' hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; **46**: 508–515.
28 Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM *et al*. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. *Am J Hypertens* 2005; **18**: 1422–1428.

Nephrol Dial Transplant (2007) 22: 911–916
doi:10.1093/ndt/gfl642
Advance Access publication 1 December 2006

NDT
Nephrology Dialysis Transplantation

Brief Report

Reverse white-coat effect as an independent risk for microalbuminuria in treated hypertensive patients

Toako Kato, Takeshi Horio, Mari Tomiyama, Kei Kamide, Satoko Nakamura, Fumiki Yoshihara, Hiroto Nakata, Hajime Nakahama and Yuhei Kawano

Division of Hypertension and Nephrology, Department of Medicine, National Cardiovascular Center, Suita, Japan

Abstract

Background. The influence of the converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension' on hypertensive target organ damage has not been fully elucidated. The present study assessed the hypothesis that this phenomenon may specifically associate with microalbuminuria, a marker of early renal damage, in treated hypertension.

Methods. A total of 267 treated essential hypertensive patients (133 men and 134 women; mean age, 66 years) without renal insufficiency or macroalbuminuria were enroled in this study. Patients were classified into three groups by the difference between office and day-time ambulatory systolic blood pressure (BP) levels; i.e. subjects with white-coat effect (W group: office − day-time systolic BP ≥20 mmHg, $n=48$), with reverse white-coat effect (R group: office − day-time systolic BP < −10 mmHg, $n=43$) and without white-coat or reverse white-coat effect (N group: −10 mmHg ≤ office − day-time systolic BP <20 mmHg, $n=176$). The urinary albumin (U-Alb) level was measured as the albumin to creatinine excretion ratio in the urine. Microalbuminuria was defined as U-Alb of ≥30 and <300 mg/g Cr.

Results. R group had a well-controlled office BP (130/77 mmHg), but their day-time BP (148/87 mmHg) was elevated compared with the other two groups. The levels of U-Alb excretion in N group, W group and R group were 12.3 (8.4, 25.6), 16.0 (10.5, 31.7) and 24.3 (10.2, 79.7) mg/g Cr [median (interquartile range)], respectively. Both U-Alb level and prevalence of microalbuminuria were significantly greater in R group than in N group. Multivariate analyses revealed that the presence of reverse white-coat effect, but not white-coat effect, was a significant predictor for microalbuminuria, independent of various clinical variables including ambulatory BP levels (odds ratio 2.63 *vs* N group, $P=0.02$).

Conclusion. These findings suggest that the presence of reverse white-coat effect may be an independent risk for early renal damage in treated hypertensive patients.

Keywords: ambulatory blood pressure monitoring; hypertension; microalbuminuria

Introduction

Ambulatory blood pressure (BP) is an important determinant of target organ damage and a significant predictor for cardiovascular morbidity and mortality in hypertensive patients [1–6]. There is often a discrepancy between office and ambulatory BPs, and many studies have investigated the association between white-coat hypertension, a normal ambulatory but elevated office BP, and cardiovascular risk [7,8]. On the other hand, the converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension', i.e. a high ambulatory but normal (or well-controlled) office BP, has received little attention [9]. Whereas, some studies have revealed that the proportion of subjects with reverse white-coat effect evaluated by the difference between office and ambulatory BPs is 20–40% in the general population and hypertensives [10,11]. In treated hypertensive patients with this phenomenon, particularly, the chance of active and sufficient antihypertensive treatment may be lost by an apparent well-controlled BP in the office. Recent studies suggested that an elevated ambulatory or home BP despite a well-controlled office BP, is associated with poor cardiovascular prognosis in treated hypertensive patients [12,13]. However, the influence of reverse white-coat effect on target organ damage in treated hypertension has remained to be elucidated.

Microalbuminuria, which is one of the early end-organ changes observed in hypertensives, has been shown to be a significant risk for not only renal

Correspondence and offprint requests to: Takeshi Horio, MD, Division of Hypertension and Nephrology, Department of Medicine, National Cardiovascular Center, 5-7-1, Fujishirodai, Suita, Osaka 565-8565, Japan. Email: thorio@ri.ncvc.go.jp

insufficiency but also cardiovascular events [14,15]. Thus, the present study was aimed to investigate the association of reverse white-coat effect with microalbuminuria as a sensitive marker of target organ damage in treated hypertensive patients.

Methods

Subjects

From 314 consecutive patients with essential hypertension who were chronically treated and underwent a 24-h ambulatory BP monitoring at an outpatient clinic of our hospital between May 2000 and December 2003, 267 subjects [133 men and 134 women; age, 30–90 years (mean, 66 years)] in whom urinary albumin (U-Alb) data were simultaneously obtained were enroled in our retrospective study. Patients with secondary hypertension, stroke, ischaemic heart disease including myocardial infarction, congestive heart failure or insulin-treated diabetes mellitus were excluded from this study. Individuals with chronic glomerulonephritis, nephrotic syndrome, renal insufficiency (serum creatinine $\geq$1.5 mg/dl), or macroalbuminuria (described later) were also excluded. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria, such as a fasting plasma glucose of $\geq$126 mg/dl and/or a plasma glucose level at 2 h after a 75 g oral glucose load of $\geq$200 mg/dl, or when medication was taken for treatment of hyperglycaemia. A diagnosis of hyperlipidaemia required a serum total cholesterol level of $\geq$220 mg/dl and/or a serum triglyceride level of $\geq$150 mg/dl or the use of lipid-lowering drugs.

All patients had taken antihypertensive drugs for at least 1 year (average, 12 years). A total of 185 (69%) were treated with Ca channel blockers, 86 (32%) with angiotensin II receptor blockers, 41 (15%) with angiotensin-converting enzyme inhibitors, 83 (31%) with β-blockers, 51 (19%) with diuretics and 27 (10%) with other classes of agents. All subjects gave their informed consent to participate in the present study. All procedures of the present study were carried out in accordance with institutional and national ethical guidelines for human studies.

Measurement of BP

In each visit, office BP was measured twice by a physician in a hospital outpatient clinic with the patient in a sitting position after over 20 min of rest, using an appropriate-size arm cuff and mercury sphygmomanometer. The first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Office BP was determined by averaging six measurements taken on three separate occasions during a 3-month period.

In the same study period, all subjects underwent 24-h ambulatory BP monitoring. BP was measured every 30 min during the day and night by the oscillometric method using an automatic monitoring device (TM-2421, A&D Co Ltd, Tokyo, Japan) [16]. The accuracy and performance of this device have been demonstrated previously [17]. The patients were instructed to carry on with their normal daily activities during measurements and note their activity and location in a diary. According to the diary, day-time and night-time were determined as the waking and sleeping periods of the patient, respectively, and mean values of 24-h, day-time and night-time BPs (systolic and diastolic) were calculated. Nocturnal BP dipping was determined as 100 × (day-time BP–night-time BP)/day-time BP.

In the present study, all subjects were classified into three groups by the difference between office and day-time ambulatory systolic BP levels according to some previous studies [10,11,18], with minor modifications; that is, subjects with overt white-coat effect (W group: office systolic BP – day-time systolic BP $\geq$20 mmHg), with overt reverse white-coat effect (R group: office systolic BP – day-time systolic BP <-10 mmHg) and with neither white-coat nor reverse white-coat effect (N group: -10 mmHg $\leq$ office systolic BP – day-time systolic BP $<$20 mmHg).

Biochemical measurement

Blood samples were obtained in the morning after an overnight fast. Fasting plasma glucose, haemoglobin A_{1c}, total cholesterol, triglycerides and serum creatinine levels were determined by standard laboratory measurements. Creatinine clearance was calculated from the Cockcroft and Gault formula [19]. The U-Alb level was measured as the albumin to creatinine excretion ratio (mg/g Cr) in the urine. Mircoalbuminuria was defined as U-Alb of $\geq$30 and $<$300 mg/g Cr. Patients with macroalbuminuria (U-Alb $\geq$300 mg/g Cr) were excluded from the study.

Statistical analysis

Statistical analysis was performed using StatView Version 5.0 Software (Abacus Concepts Inc., Berkeley, CA, USA). Values are expressed as mean ± SE, except for U-Alb, and frequencies are expressed as percentages. Levels of U-Alb are given as median and interquartile range (25–75th percentiles). The significance of differences among the three groups (N group, W group and R group) was evaluated by an unpaired ANOVA with subsequent Scheffe's multiple comparison test. Due to skewed distribution, U-Alb levels were analysed by a non-parametric Kruskal–Wallis test. In addition, log-transformed U-Alb levels were used for comparison between groups or for correlation analysis. Simple correlations between log-transformed U-Alb and BP parameters were assessed using univariate linear regression analyses and Pearson's correlation coefficient. A multiple logistic regression analysis was used to identify independent determinants of microalbuminuria. A value of $P < 0.05$ was accepted as statistically significant.

Results

Clinical characteristics of the three subject groups classified according to the difference between office and day-time ambulatory systolic BP levels are summarized in Table 1. Forty-eight (18.0%) and 43 (16.1%) patients were identified as having overt white-coat effect (W group) and reverse white-coat effect (R group), respectively, and the other 176 (65.9%) patients belonged to N group. The proportion of men was higher and body mass index was greater in R group compared with W group.

Table 1. Clinical characteristics of study subjects

Variable	N group ($n=176$)	W group ($n=48$)	R group ($n=43$)
Age, years	65.3 ± 0.8	68.1 ± 1.2	64.2 ± 1.7
Sex (men),%	50.6	33.3	65.1†
Body mass index, kg/m^2	24.3 ± 0.3	23.5 ± 0.4	25.5 ± 0.7†
Duration of hypertension, years	18.2 ± 0.8	21.4 ± 1.4	14.4 ± 1.4†
Diabetes mellitus,%	19.9	16.7	14.0
Hyperlipidaemia,%	64.6	75.0	74.4
Current smoking,%	14.9	18.8	23.3
Serum creatinine, mg/dl	0.75 ± 0.02	0.69 ± 0.03	0.78 ± 0.03
Creatinine clearance, ml/min	84.4 ± 2.0	81.7 ± 3.9	92.3 ± 5.8
Fasting plasma glucose, mg/dl	102 ± 2	105 ± 3	101 ± 3
Haemoglobin A_{1c},%	5.5 ± 0.1	5.7 ± 0.1	5.6 ± 0.1
Total cholesterol, mg/dl	203 ± 2	204 ± 3	200 ± 3
Triglycerides, mg/dl	121 ± 5	126 ± 15	140 ± 9
Antihypertensive treatment			
Period of medication, years	12.4 ± 0.7	15.1 ± 1.4	9.3 ± 1.1†
AII receptor blockers,%	33.5	27.1	32.6
ACE inhibitors,%	17.0	10.4	14.0
Ca channel blockers,%	67.6	68.8	76.7
β-Blockers,%	29.0	41.7	27.9
α-Blockers,%	10.8	8.3	9.3
Diuretics,%	18.8	20.8	18.6
Total number of classes	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
Office systolic BP, mmHg	142.0 ± 0.8	165.4 ± 2.0*	129.7 ± 1.5*,†
Office diastolic BP, mmHg	82.5 ± 0.7	91.0 ± 1.7*	76.9 ± 1.3*,†
Day-time systolic BP, mmHg	137.1 ± 0.8	132.4 ± 1.7*	148.0 ± 1.5*,†
Day-time diastolic BP, mmHg	80.9 ± 0.7	78.6 ± 1.5	87.0 ± 1.5*,†
Night-time systolic BP, mmHg	127.6 ± 1.1	124.4 ± 2.2	136.0 ± 2.4*,†
Night-time diastolic BP, mmHg	74.0 ± 0.8	72.6 ± 1.7	78.0 ± 1.5†
24-h systolic BP, mmHg	134.7 ± 0.9	130.9 ± 1.7	143.9 ± 1.6*,†
24-h diastolic BP, mmHg	78.9 ± 0.7	76.6 ± 1.6	84.1 ± 1.3*,†
Nocturnal systolic BP dipping,%	6.9 ± 0.6	6.1 ± 1.1	8.2 ± 1.1
Nocturnal diastolic BP dipping,%	8.3 ± 0.7	7.6 ± 1.1	10.0 ± 1.2

Values are mean ± SE or percentage. *$P < 0.05$ *vs* N group; †$P < 0.05$ *vs* W group.
AII, angiotensin II; ACE, angiotensin-converting enzyme; BP, blood pressure.

Duration of hypertension and period of medication were significantly shorter in R group than in W group. The prevalence of diabetes mellitus and hyperlipidaemia, the rate of current smokers, renal function and glucose and lipid parameters did not differ among the three groups. In addition, no intergroup differences were found in the use of any class of antihypertensive agent including angiotensin II receptor blocker and angiotensin-converting enzyme inhibitor and total number of classes of antihypertensive drugs.

Office systolic and diastolic BPs were significantly higher in W group and lower in R group compared with N group. Day-time, night-time and average 24-h ambulatory BPs were significantly elevated in R group than in the other two groups. There were no significant differences in ambulatory BPs between N group and W group, except that day-time systolic BP was somewhat lower in W group than in N group. The degree of nocturnal BP dipping, an index of circadian BP variation, did not differ among the three groups.

The U-Alb levels in N group, W group and R group were 12.3 (8.4, 25.6), 16.0 (10.5, 31.7) and 24.3 (10.2, 79.7) mg/g Cr, respectively, indicating that R group had a significantly higher level of U-Alb compared with N group (Figure 1A). The percentage of patients with microalbuminuria was also significantly higher in R group than in N group (Figure 1B). U-Alb level and prevalence of microalbuminuria in W group did not differ from those in N group.

To avoid the influence of diabetes mellitus or the specific effect of renin–angiotensin system (RAS) inhibitors (i.e. angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors) on U-Alb excretion, we re-examined the U-Alb level after excluding some subjects. Even after excluding patients with diabetes mellitus ($n=218$), U-Alb level was significantly increased in R group than in N group [24.3 (10.5, 73.8) and 11.5 (7.6, 24.2) mg/g Cr, $P=0.0024$]. Likewise, even after excluding patients receiving RAS inhibitors ($n=141$), U-Alb level in R group was still higher compared with that in N group [36.5 (19.0, 101.3) and 12.1 (8.7, 26.2) mg/g Cr, $P=0.0004$].

Simple correlations of office and ambulatory BPs with U-Alb levels were examined in all 267 subjects. Although office systolic or diastolic BP had no correlation with log-transformed U-Alb level (data not shown), log U-Alb was positively correlated with ambulatory systolic BP during day-time ($r=0.272$, $P<0.0001$), night-time ($r=0.230$, $P=0.0001$),

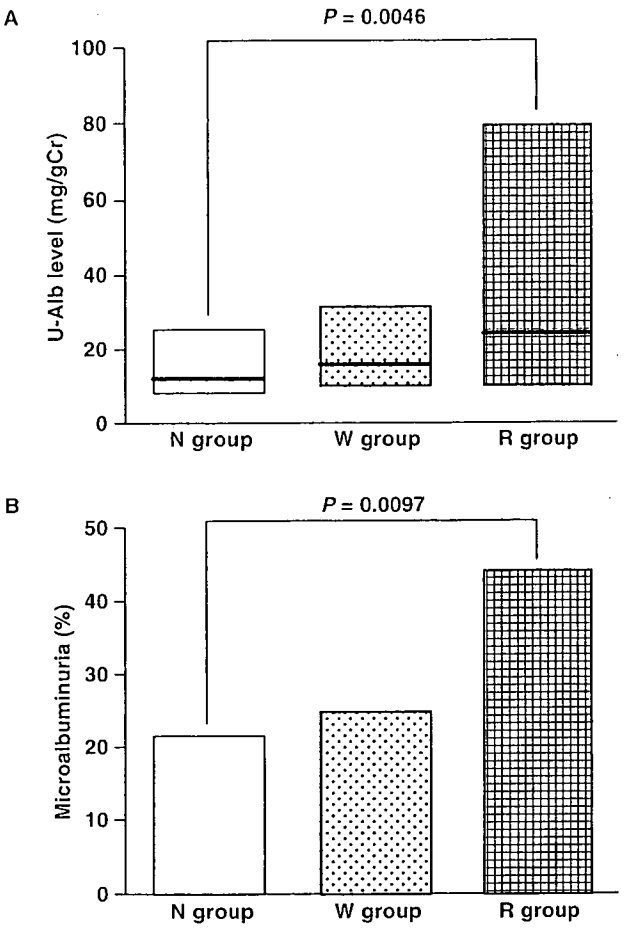

Fig. 1. U-Alb levels (A) and prevalence of microalbuminuria (B) in the three groups classified by the difference between office and day-time systolic BP levels. Values are given as median and interquartile range (25th–75th percentiles) (A) or percentage (B). Due to skewed distribution, U-Alb levels were analysed by a non-parametric Kruskal–Wallis test ($P=0.0095$). Log-transformed U-Alb levels were used for comparison between groups.

and 24 h ($r=0.246$, $P<0.0001$). The difference between office and day-time systolic BP tended to correlate inversely with log U-Alb, but it was not statistically significant ($r=-0.114$, $P=0.0628$).

To confirm whether the influence of reverse white-coat phenomenon on U-Alb excretion was independent of various clinical parameters including ambulatory BP levels, we investigated possible predictive factors using a multiple logistic regression analysis in all subjects. As shown in Table 2, the presence of reverse white-coat effect (i.e. R group) was found to be a significant predictor for microalbuminuria, independent of age, sex, hypertension duration, use of RAS inhibitor, complication of diabetes mellitus, renal function (creatinine clearance) and day-time average systolic and diastolic BP levels [odds ratio (OR) 2.627 *vs* N group, $P=0.0197$]. The presence of white-coat effect (i.e. W group) was not an independent determinant of microalbuminuria (OR 1.163 *vs* N group, $P=0.7125$). The significant predictive value of reverse white-coat effect remained even though average 24-h systolic and diastolic BPs, instead of day-time BPs, were adopted as independent predictors (data not shown).

Table 2. Independent predictors for microalbuminuria by multiple logistic regression analysis

Variable	OR (95% CI)	*P*-value
Age, 10 years	1.014 (0.675–1.523)	0.9473
Sex, men	0.962 (0.513–1.803)	0.9029
Duration of hypertension, 1 year	1.037 (1.007–1.068)	0.0167
Use of RAS inhibitor, yes	0.509 (0.276–0.937)	0.0301
Diabetes mellitus, yes	1.473 (0.679–3.193)	0.3268
Creatinine clearance, 10 ml/min	0.939 (0.821–1.074)	0.3552
Day-time systolic BP, 10 mmHg	1.491 (1.098–2.023)	0.0105
Day-time diastolic BP, 10 mmHg	0.947 (0.653–1.374)	0.7749
BP pattern		
N group (normal type)	1 (reference)	
W group (white-coat effect)	1.163 (0.521–2.596)	0.7125
R group (reverse white-coat effect)	2.627 (1.167–5.916)	0.0197

RAS inhibitor represents angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor.
CI, confidence interval; RAS, renin–angiotensin system; BP, blood pressure.

Discussion

This study has demonstrated that the presence of reverse white-coat effect is one of the independent predictors for microalbuminuria in patients with treated essential hypertension. Our study provided the novel findings to prove the significant association of reverse white-coat phenomenon with U-Alb excretion in essential hypertension, because the relation between reverse white-coat hypertension (or masked hypertension) and early renal damage such as microalbuminuria in hypertensive subjects has not been elucidated.

In the present study, subjects with reverse white-coat effect (R group) had a well-controlled office BP (<130/80 mmHg) in spite of elevated ambulatory BP, suggesting that R group took on an aspect of masked hypertension. There have been a few studies reporting the possible association between masked hypertension and cardiac and carotid arterial structural changes. Liu *et al.* [20] originally found that left ventricular mass and carotid wall thickness in subjects with masked hypertension were significantly greater than those in true normotensive subjects and similar to those in patients with sustained hypertension. Another study also showed that left ventricular mass index and prevalence of left ventricular hypertrophy were increased in untreated subjects with masked hypertension and sustained hypertension than in those with true normotension [21]. Therefore, the present findings

were broadly consistent with these previous observations concerning the association between masked hypertension and target organ damage. Recent prospective studies revealed that a high ambulatory or home BP is a powerful predictor for cardiovascular morbidity and mortality in the general population and treated hypertensive patients even when their office BP is normal or well controlled [12,13,22–24]. Taken together, it is likely that advanced target organ changes in patients with masked hypertension or reverse white-coat condition are linked to poor cardiovascular prognosis in such patients.

A higher level of ambulatory BP is a major determinant of target organ damage in hypertensive patients [1,2]. In the present study, average levels of day-time, night-time and 24-h ambulatory BPs were the highest in R group. Whereas, since the association of reverse white-coat effect with microalbuminuria was still significant after adjusted for average day-time (or 24-h) BP levels, our results suggest that other factors than a higher ambulatory BP could contribute to target organ damage in reverse white-coat hypertension. A shorter period of antihypertensive medication might partially explain the advanced end-organ change in the present subjects with reverse white-coat effect. However, our study has not provided the specific mechanism by which reverse white-coat effect could promote renal damage in patients with treated hypertension. Further investigations are required to clarify how reverse white-coat or masked hypertension has a specific unfavourable effect on the hypertensive target organ.

There were some limitations in our study. Considering the intra-individual variability of U-Alb level, the evaluation of albuminuria using a single urine collection might underestimate the prevalence of microalbuminuria and weaken the relationship between U-Alb and patterns of BP variation. In addition, our subjects were divided into subgroups on the basis of office–day-time systolic BP difference obtained from one-time examination of ambulatory BP monitoring. A reverse white-coat phenomenon is usually identified as an office BP lower than day-time (or 24-h) ambulatory BP [10,11]. In the present study, however, it was defined as office–day-time systolic BP of <-10 mmHg to detect only overt reverse white-coat effect from one-time monitoring of ambulatory BP.

All patients in the present study had received antihypertensive medication. As another limitation of this study, therefore, we must consider the possibility that different classes of antihypertensive drugs may have differently affected U-Alb excretion. RAS inhibitors, particularly, are known to have BP fall-independent protective effects against renal damage. However, the percentage of patients treated with angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors did not differ among the three study groups. Our multivariate analysis also showed that the relation of reverse white-coat effect to microalbuminuria was independent of the use of RAS inhibitors. Nonetheless, since BP reduction *per se*, regardless of classes of antihypertensive drugs, decreases U-Alb excretion, the determination of U-Alb level under drug-free period might be more desirable to evaluate the basal renal damage.

In conclusion, the present study indicates that reverse white-coat effect is a significant predictor for microalbuminuria in patients with treated essential hypertension, independent of average ambulatory BP levels and various other clinical risk factors. Our findings suggest that the presence of this phenomenon may be an independent risk for early renal damage in treated hypertensive patients and ambulatory BP monitoring (or home BP measurement) seems to be necessary to unmask this latent risk that is not detectable by routine BP measuring in the office.

Acknowledgements. This study was supported by the Grant for Cardiovascular Disease (11C-5) and the Health and Labor Sciences Research Grants (H14-kouka-021) from the Ministry of Health, Labor and Welfare of Japan and the Grant from Japan Cardiovascular Research Foundation. We thank Chikako Tokudome, Yoko Oikawa and Yoko Saito for their secretarial assistance.

Conflict of interest statement. None declared.

References

1. Pickering TG, Harshfield GA, Devereux RB, Laragh JH. What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension* 1985; 7: 171–177
2. Schillaci G, Verdecchia P, Sacchi N *et al.* Clinical relevance of office underestimation of usual blood pressure in treated hypertension. *Am J Hypertens* 2000; 13: 523–528
3. Cuspidi C, Meani S, Fusi V *et al.* Isolated ambulatory hypertension and changes in target organ damage in treated hypertensive patients. *J Hum Hypertens* 2005; 19: 471–477
4. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA* 1983; 249: 2792–2798
5. Staessen JA, Thijs L, Fagard R *et al.* Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; 282: 539–546
6. Verdecchia P, Reboldi G, Porcellati C *et al.* Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *J Am Coll Cardiol* 2002; 39: 878–885
7. Palatini P, Mormino P, Santonastaso M *et al.* Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension: results from the HARVEST study. *Hypertension* 1998; 31: 57–63
8. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998; 98: 1892–1897
9. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension* 2002; 40: 795–796
10. Wing LMH, Brown MA, Beilin LJ, Ryan P, Reid CM. 'Reverse white-coat hypertension' in older hypertensives. *J Hypertens* 2002; 20: 639–644
11. Bombelli M, Sega R, Facchetti R *et al.* Prevalence and clinical significance of a greater ambulatory versus office blood pressure ('reversed white coat' condition) in a general population. *J Hypertens* 2005; 23: 513–520
12. Clement DL, De Buyzere ML, De Bacquer DA *et al.* Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; 348: 2407–2415