O R I G I N A L A R T I C L E

Prevalence and significance of white-coat hypertension and masked hypertension in type 2 diabetics

| | | CME |
|---|------------|--|
| CM Ng 伍超明 SF Yiu 姚少峰 KL Choi 蔡建霖 CH Choi 蔡祥熙 | Objectives | To explore the prevalence of various categories of hypertension in diabetic patients, and assess any corresponding associations with end-organ complications. |
| YW Ng 伍英偉 | Design | Cross-sectional study. |
| SC Tiu 張秀祥 | Setting | Tertiary centre of a regional hospital in Hong Kong. |
| | Patients | All ambulatory type 2 diabetic patients attending our clinics from January 2002 to November 2004 were invited to participate in the protocol. |
| | Results | A total of 133 diabetic patients were included; 82 had normal clinic blood pressures, 15 (18%) of whom had masked hypertension, the remaining 67 (82%) had 'normotension'. The remaining 51 patients had high clinic blood pressures, of whom 28 (55%) had white-coat hypertension and 23 (45%) had sustained hypertension. Urinary albumin excretion rate was higher in patients with masked hypertension (10 mg/day; range, 7-580 mg/day) and sustained hypertension (7 mg/day; 7-360 mg/day) in comparison to those with white-coat hypertension (7 mg/day; 7-109 mg/day) or 'normotension' (7 mg/day; 7-181 mg/day) [P<0.01]. Likewise, the prevalence of albuminuria was significantly higher in patients with masked hypertension (11%) [P<0.01]. The prevalence of left ventricular hypertrophy was significantly higher in subjects with masked hypertension (38%) and sustained hypertension (26%) compared to patients with 'normotension' (8%) or white-coat hypertension (11%) [P<0.01]. Left ventricular diastolic dysfunction was more prevalent in patients with masked hypertension (48%), and white-coat hypertension (48%), and white-coat hypertension (48%), in comparison to subjects with 'normotension' (18%) [P=0.01]. |
| Key words Ibuminuria; Blood pressure monitoring, ambulatory; Diabetes mellitus, type 2; Hypertension | | Masked hypertension is associated with a higher prevalence of albuminuria, left ventricular diastolic dysfunction, and hypertrophy. White-coat hypertension carries a more benign prognosis than sustained hypertension and masked hypertension. Our cross-sectional study supports the recommendation to performing ambulatory blood pressure measurements in type 2 diabetic patients. |
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Albuminuria:

Department of Medicine, Queen Elizabeth Hospital, Kowloon, Hong Kong CM Ng, MRCP, FHKAM (Medicine) *SF Yiu, FRCP (Glasg, Edin), FHKAM (Medicine) *KL Choi, FRCP (Glasg, Edin), FHKAM (Medicine) CH Choi, MRCP, FHKAM (Medicine)

YW Ng, MRCP, FHKAM (Medicine) SC Tiu, FRCP (Lond, Edin), MD

* Current affiliation: Private specialist

Correspondence to: Dr CM Ng E-mail: ngcm2@ha.org.hk

Introduction

Traditionally, hypertension was defined by elevated blood pressure measurements in a medical setting. As technology enables user-friendly measurement of blood pressure in ambulatory and home settings, new categories of hypertension have become evident, notably white-coat hypertension and masked hypertension. However, the clinical significance of these categories is not well defined.

In view of the significance of blood pressure control in preventing long-term complications of diabetes,^{1,2} we designed a clinical protocol for more detailed blood pressure assessment in type 2 diabetic patients newly referred to our clinics. Our objectives were to (1) identify the prevalence of various categories of hypertension in the diabetic population, and (2) assess the association of these categories of hypertension with end-

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白袍高血壓和隱性高血壓在二型糖尿病患者 中的現患率及重要性

- 目的 探討糖尿病患者中不同種類高血壓的現患率,以及它 們與終末器官併發症的關係。
- 設計 橫斷面研究。
- 安排 香港一所地區醫院的三級轉介中心。
- **患者** 所有於2002年1月至2004年11月到我們診所的二型糖 尿病患者,都被邀請參與研究。
- 結果 共133位糖尿病患者中,82位有正常診所血壓,其中 15位(18%)有隱性高血壓,其餘67位(82%)血壓 「正常」。另51位有高診所血壓,其中28位(55%) 有白袍高血壓,23位(45%)有持續性高血壓。在 尿蛋白排泄率方面,隱性高血壓患者(10 mg/d,7-580 mg/d)及持續性高血壓患者(7 mg/d, 7-3360 mg/d)都比白袍高血壓患者(7 mg/d, 7-109 mg/d) 及血壓「正常」的病人(7 mg/d, 7-181 mg/d) 顯著 較高(P<0.01)。同樣地,在蛋白尿方面,隱性高血 壓患者(40%)及持續性高血壓患者(26%)都比血 壓「正常」的病人(6%)及白袍高血壓患者(11%) 顯著較高(P<0.01)。而在高血壓左室肥厚發生率 方面,隱性高血壓患者(38%)及持續性高血壓患者 (26%)比血壓「正常」的病人(8%)及白袍高血壓 患者(11%)顯著較高(P<0.01)。在左心室舒張功能 損害程度上,隱性高血壓患者(46%)、持續性高血壓 患者(48%),以及白袍高血壓患者(43%)都比血壓 「正常」的病人(18%)顯著嚴重(P=0.01)。
- 結論 隱性高血壓與高蛋白尿及左心室舒張功能損害相關。 與持續性高血壓及隱性高血壓比較,白袍高血壓預後 較好。本橫斷面研究支持為二型糖尿病患者量度動態 血壓的建議。

organ complications.

Methods

All ambulatory type 2 diabetic patients attending our clinics from January 2002 to November 2004 were invited to participate in the protocol for more detailed assessment for hypertension. Patients who were unwilling to participate, who required insulin therapy, who had unstable diabetic control, who had known autonomic neuropathy, or who were taking anti-hypertensive medications for either hypertension or other conditions (eg alpha-blocker for prostatic problems or angiotensin-converting enzyme inhibitor for heart failure) were excluded. All subjects gave verbal informed consent to avail of this clinical service.

Blood pressure assessment protocol

For all subjects, clinic blood pressure (CBP) measurement was performed six times, thrice each

on two different clinic visits. At each visit, blood pressure was taken in the clinic after the subject had rested for 15 minutes after arrival. The seated subject was advised to place the arm horizontally on the table, at the level of the heart, and the blood pressure was measured in the non-dominant arm by a nurse, using an automated blood pressure machine (Dinamap 1846SX; Critikon, Florida, US). The same nurse measured the blood pressure again before the medical consultation, and a third time after the consultation process.

Ambulatory blood pressure (ABP) measurement at 30-minute intervals during day and night was arranged for all subjects between the two clinic visits, and within 1 month of the first clinic visit. Tracker non-invasive blood pressure with an oscillometric technique was employed in our hospital for this purpose. A cuff appropriate to the circumference of the patient's arm was attached to the non-dominant arm at around 11 am on the day of ABP measurement and kept in situ for around 25 hours. Patients were instructed as described in the manual of the device.³ They were also advised to continue with their normal daily activities and exercise between measurements, and keep a log when they retired to bed and woke up.

All patients were examined for the presence of any retinopathy and had their body mass index, renal function, fasting sugar and lipids, glycosylated haemoglobin, and 24-hour urine albumin measured within 12 weeks of the first clinic visit. Urine albumin was measured using an immunoturbidimetric assay (Modular Analytics; Roche Diagnostics, Mannheim, Germany). The lower limit of detection by our assay was 7 mg/day; all urine albumin values of lower than 7 mg/day were taken to be 7 mg/day. Transthoracic echocardiography was performed on each patient, according to the recommendations of the American Society of Echocardiography.⁴ Ejection fraction was assessed by Simpson's method. Left ventricular hypertrophy was determined by measuring posterior free wall and septal wall thickness by M-mode study. The ratio of the velocity of the early-to-late filling wave was derived from Doppler interrogation of left ventricular inflow, and deemed to be a measure of diastolic function. Echocardiography was performed by the same cardiologist, who was blinded to the results of the patient's blood pressure and other parameters.

Analysis

The following parameters were calculated from the recorded values: 24-hour, wake-time, and sleep-time mean blood pressures—wake time was defined as the period when the patient was awake, and sleep time as that between retiring to bed and waking up in the morning.

| | 'Normotension' (n=67) | Masked hypertension (n=15) | White-coat hypertension (n=28) | Sustained hypertension (n=23) | P value |
|-------------------------------------|--------------------------|-------------------------------|-----------------------------------|----------------------------------|---------|
| Age (years) | 53±11 | 53±11 | 59±11 | 58±12 | 0.05 |
| Male subjects | 38 | 11 | 17 | 16 | 0.54 |
| Duration of diabetes (years) | 9±6 | 11±7 | 8±4 | 10±6 | 0.42 |
| BMI (kg/m²) | 25±4 | 26±3 | 26±5 | 26±4 | 0.71 |
| Body weight (kg) | 64±14 | 69±10 | 67±14 | 72±16 | 0.14 |
| Waist-hip ratio | 0.90 (0.75-1.03) | 0.91 (0.83-1.04) | 0.92 (0.78-1.00) | 0.93 (0.83-1.00) | 0.02 |
| HbA _{1c} (%) | 7.6±1.6 | 8.1±1.7 | 7.8±1.7 | 7.5±1.5 | 0.63 |
| Total cholesterol (mmol/L) | 5.0±1.1 | 5.0±0.8 | 5.3±0.9 | 5.2±0.8 | 0.46 |
| LDL cholesterol (mmol/L) | 2.9±0.8 | 2.8±0.5 | 3.2±0.9 | 3.0±0.7 | 0.39 |
| HDL cholesterol (mmol/L) | 1.3±0.3 | 1.3±0.3 | 1.4±0.3 | 1.3±0.2 | 0.82 |
| Triglycerides (mmol/L) | 1.6±1.3 | 1.8±1.6 | 1.7±0.8 | 2.2±1.4 | 0.34 |
| Creatinine (µmol/L) | 81±15 | 85±12 | 83±17 | 86±16 | 0.43 |
| Smokers | 11 | 5 | 2 | 3 | 0.37 |
| History of CVA | 1 | 2 | 0 | 1 | 0.07 |
| History of PVD | 1 | 0 | 1 | 0 | 0.71 |
| DMR | 1 | 0 | 2 | 3 | 0.10 |
| HTR | 0 | 1 | 0 | 0 | NA |
| Hypoglycaemia during ABP monitoring | 7 | 1 | 0 | 2 | 0.35 |

TABLE I. Clinical and biochemical parameters of subjects stratified according to hypertensive categories*+

* ABP denotes ambulatory blood pressure, BMI body mass index, CVA cerebrovascular accident, DMR diabetic retinopathy, HbA_{1C} glycosylated haemoglobin, HDL high-density lipoprotein, HTR hypertensive retinopathy, LDL low-density lipoprotein, NA not applicable, and PVD peripheral vascular disease

⁺ Data are shown as number, mean±standard deviation, or median (range)

Normal ABP was defined according to American Heart Association recommendations in 2005.⁵ Ambulatory blood pressure was considered to be high if (i) the wake-time mean blood pressure was >140/90 mm Hg, (ii) the sleep-time mean blood pressure was >125/75 mm Hg, or (iii) the 24-hour mean blood pressure was >135/85 mm Hg. Clinic blood pressure was defined as the mean of the six blood pressure measurements taken during the two clinic visits. Normal CBP was defined as a systolic blood pressure of <140 mm Hg and a diastolic blood pressure of <90 mm Hg.

Subjects were classified into four hypertensive categories according to the values of ABP and CBP: (1) 'normotension': normal CBP and ABP; (2) masked hypertension: normal CBP and elevated ABP; (3) white-coat hypertension: elevated CBP and normal ABP; and (4) sustained hypertension: elevated CBP and ABP.

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], US). All continuous variables were expressed as either mean ± standard deviation for parametric data or median (range) for non-parametric data. The Chi squared was applied to test for independence between categorical variables in the four hypertensive groups. For continuous variables, one-way analysis of variance was employed

for parametric data and the Kruskal-Wallis test for non-parametric data. Bivariate Pearson correlation matrices were used to obtain the correlation coefficients. All statistical tests were two-sided, with an alpha level of 0.05.

Results

A total of 133 type 2 diabetic patients participated in the study. Echocardiographic results were available in 129 of them. Of the 133 subjects, 82 had normal CBP, 15 (18%) of whom had masked hypertension, the remaining 67 (82%) had 'normotension'. In all, 51 subjects had high CBP; 28 (55%) had whitecoat hypertension and 23 (45%) had sustained hypertension.

The characteristics of the study subjects and their blood pressure readings are shown in Tables 1 and 2 respectively. There were no statistically significant differences among the four groups with regard to gender, duration of diabetes, co-morbidities, body mass index, body weight, serum creatinine, glycaemic and lipid profiles. The median waist-hip ratio in subjects with sustained hypertension was higher than that in those with 'normotension' (0.93; range, 0.83-1.00 vs 0.90; 0.75-1.03) [P=0.02]. The mean age for patients with white-coat hypertension was higher than those with masked hypertension (59±11

| TABLE 2. Results of ambulatory and clinic blood pressure (mm Hg) and blood pressure loads (%) in subjects stratified according to different |
|---|
| hypertensive categories* |

| Category of | Mean±SD | | | | | |
|-------------------------------|---------|---|--------|------------------------|-------|--|
| blood pressure 'Normotension' | | Masked hypertension White-coat hypertension | | Sustained hypertension | | |
| Clinic | | | | | | |
| SBP | 122±11 | 129±8 | 154±11 | 157±16 | <0.01 | |
| DBP | 72±6 | 76±6 | 82±7 | 88±8 | <0.01 | |
| 24-Hour | | | | | | |
| SBP | 113±10 | 129±7 | 121±6 | 135±10 | <0.01 | |
| DBP | 71±6 | 81±3 | 74±6 | 85±6 | <0.01 | |
| Wake-time | | | | | | |
| SBP | 118±10 | 133±9 | 125±7 | 138±12 | <0.01 | |
| DBP | 74±7 | 84±6 | 77±7 | 88±7 | <0.01 | |
| SBP load | 9±12 | 24±23 | 13±10 | 45±32 | <0.01 | |
| DBP load | 7±11 | 25±30 | 11±13 | 44±26 | <0.01 | |
| Sleep-time | | | | | | |
| SBP | 101±19 | 122±7 | 112±7 | 129±9 | <0.01 | |
| DBP | 63±10 | 77±3 | 67±6 | 78±7 | 0.01 | |
| SBP load | 6±12 | 42±24 | 16±16 | 64±25 | <0.01 | |
| DBP load | 5±11 | 39±17 | 9±12 | 46±29 | <0.01 | |

* SBP denotes systolic blood pressure, and DBP diastolic blood pressure

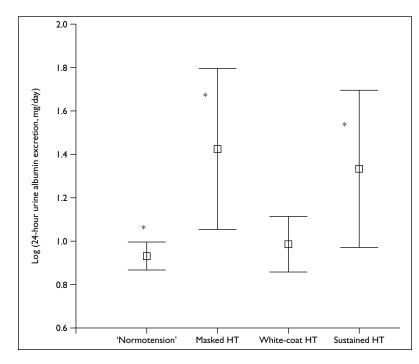


FIG. 24-Hour urinary albumin excretion in patients stratified according to hypertensive categories $% \label{eq:field} \label{eq:field}$

HT denotes hypertension

* P<0.01 when compared to 'normotension'

vs 53 \pm 11 years), at a borderline significance level of P=0.05.

The urinary albumin excretion rate was higher in patients with masked hypertension (10 mg/day;

range, 7-580 mg/day) and sustained hypertension (7 mg/day; range, 7-3360 mg/day) than in those with white-coat hypertension (7 mg/day; range, 7-109 mg/day) or 'normotension' (7 mg/day; range, 7-181 mg/day) [P<0.01, Fig]. Likewise, the prevalence of albuminuria (microalbuminuria or macroalbuminuria) was significantly greater in patients with masked hypertension (40%) and sustained hypertension (26%) than in those with 'normotension' (6%) or white-coat hypertension (11%) [P<0.01, Table 3].

The correlations between 24-hour urinary albumin excretion and the clinic, 24-hour, waketime, and sleep-time systolic blood pressures were 0.13 (P=0.125), 0.23 (P=0.009), 0.17 (P=0.049), and 0.21 (P=0.014), respectively. The correlations between 24-hour urinary albumin excretion and clinic, 24-hour, wake-time, sleep-time diastolic blood pressures were 0.21 (P=0.02), 0.30 (P=0.001), 0.25 (P=0.005), and 0.21(P=0.019), respectively.

No subject had a history of myocardial infarction or echocardiographically detectable regional wall motion abnormalities. All subjects except one had normal ejection fractions. The prevalence of echocardiographic left ventricular hypertrophy was significantly higher in subjects with masked hypertension (38%) and sustained hypertension (26%) compared to those with 'normotension' (8%) or white-coat hypertension (11%) [P<0.01]. Left ventricular diastolic dysfunction as judged by impaired echocardiographic left ventricular relaxation was more prevalent in patients with

| TABLE 3 Numbers of | natients with diffe | erent degrees of 74-h | our urinary albumin | excretion according to | hypertensive category* |
|--------------------|---------------------|-----------------------|-----------------------|------------------------|------------------------|
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| Degree of urinary albumin excretion | 'Normotension' | Masked hypertension | White-coat hypertension | Sustained hypertension |
|-------------------------------------|----------------|---------------------|-------------------------|------------------------|
| Normal | 63 | 9 | 24 | 17 |
| Microalbuminuria | 4 | 5 | 3 | 3 |
| Macroalbuminuria | 0 | 1 | 0 | 3 |

* The prevalence of microalbuminuria was significantly greater in patients with masked hypertension (P<0.01) and sustained hypertension (P<0.01) than in those with 'normotension'

TABLE 4. Numbers of patients with echocardiographic evidence of left ventricular hypertrophy (LVH) and left ventricular (LV) diastolic dysfunction according to hypertensive category

| | 'Normotension' | Masked hypertension | White-coat hypertension | Sustained hypertension | P value |
|--|----------------|---------------------|-------------------------|------------------------|---------|
| Echocardiographic LVH | | | | | |
| Present | 5 | 5 | 3 | 6 | <0.01 |
| Absent | 60 | 8 | 25 | 17 | |
| Echocardiographic LV diastolic dysfunction | | | | | |
| Present | 12 | 6 | 12 | 11 | 0.01 |
| Absent | 53 | 7 | 16 | 12 | |

masked hypertension (46%), sustained hypertension (48%) and white-coat hypertension (43%) than in those with 'normotension' (18%) [P=0.01, Table 4].

Discussion

Control of hypertension is of paramount importance in the treatment of diabetes mellitus.^{6,7} How hypertension should be defined is, however, still a matter of controversy. Although blood pressure measurements are traditionally performed in medical settings, the introduction of ABP monitoring technologies has enabled measurement outside these settings. Mismatches between CBP and ABP measurements have led to conceptualisation of entities such as white-coat hypertension and masked hypertension, whose clinical significance has not been adequately studied.

The prevalence of masked hypertension in the general population has been reported to be around 10 to 20%.8-10 Among patients with diabetes, its prevalence is reported to be as high as 30 to 47%.^{11,12} In our total patient cohort of type 2 diabetics who were not taking any antihypertensive medications, the prevalence of masked hypertension was 11%. Moreover, 18% of subjects with normal CBP (defined by a mean of six CBP levels of <140/90 mm Hg) had masked hypertension. The lower prevalence rate of masked hypertension in our cohort and the widely differing prevalence rates reported in the literature could be attributed to differences in the patient populations, the number, and the way CBP measurements are performed, how ABP is measured, and the definitions used for various categories of hypertension. Unlike studies in which CBP was based on one to two measurements only,^{9,11} we used the

average of six measurements to reduce the variability and improve the accuracy of CBP determinations.¹³ Alarmingly, repeated CBP assessments could miss up to one fifth of patients with hypertension outside clinic settings.

Although the clinical significance of masked hypertension can only be definitively demonstrated with a longitudinal study, our cross-sectional data suggest that it is not a benign condition. Urinary albumin excretion (a well-recognised surrogate marker for renal injury and cardiovascular risk), left ventricular hypertrophy, and left ventricular diastolic dysfunction were all significantly more common among subjects with masked hypertension compared to those with 'normotension'. This observation is supported by findings in other studies, which showed an association between masked hypertension with high ventricular mass,¹⁴ carotid thickness,¹⁵ and cardiovascular mortality.¹⁶

Intriguingly, both the urinary albumin excretion rate and the prevalence of left ventricular hypertrophy were higher among subjects with masked hypertension than those with white-coat hypertension. The duration of exposure to a high blood pressure within a 24-hour period (equivalent to the concept of 'load' in ABP terms) may have account for this observation. However, this dichotomy was not evident for all parameters, possibly because of the relatively small sample size.

The reported prevalence rates of white-coat hypertension in the diabetic population are also quite variable. For instance, Nielsen et al¹⁷ reported a prevalence of 23% in diabetic patients with normoalbuminuria, while others reported prevalence rates as high as 51 to 62%.^{18,19} In our patient cohort, the prevalence of white-coat hypertension was 21%, whilst less than half of those who had high CBPs had sustained hypertension.

As reported by Glen et al,²⁰ we found an association with impaired left ventricular relaxation, which did not support a completely benign nature for white-coat hypertension as proposed by some investigators.²¹ Nevertheless, differentiating between white-coat hypertension and sustained hypertension may have prognostic and clinical significance. Thus, urinary albumin excretion rates and the prevalence of left ventricular hypertension were significantly lower than among those with sustained hypertension.

Whether ABP monitoring should be routinely performed among diabetic patients is still a contentious issue. While some investigators use ABP measurement as standard and consider CBP measurement is good enough, with high positive predictive value,²² increasingly there are data to support the importance of measuring blood pressure in an ambulatory setting. Factors that can affect blood pressure measurements²³ in a clinic setting are often not present in daily life, and there are good reasons to suspect that CBP may not be representative of the usual blood pressure. The development and regression of target-organ damage appears more closely associated with 24-hour or mean daytime blood pressure levels than CBP values.^{24,25} Ambulatory blood pressure levels also yield better correlations than CBP with proteinuria and other hypertensive complications during pregnancy.26 Our data in patients with type 2 diabetes showed that urinary albumin excretion was more strongly associated with ABP levels (24-hour, wake-time, or sleep-time systolic and 24-hour or wake-time diastolic) than with CBP values.

The interpretation of results from different ABP studies is fraught with difficulties, because

different cut-off values have been used by different guidelines/investigators.²⁷⁻²⁹ In our analysis, we adopted recommendations by the American Heart Association,⁵ as they are among the most established and authoritative on hypertension. According to the latter, there are grey-zone blood pressure values that lie between 'normal' and 'abnormal'. Since there is as yet no information on the significance of this 'greyzone'.³⁰ for the sake of this analysis we decided to treat these values as normal. Another area of contention in ABP interpretation is whether wake-time, sleep-time, or 24-hour mean blood pressure values are more informative.³¹ We defined ABP to be normal, only when wake-time, sleep-time, as well as 24-hour mean blood pressure levels were all within normal ranges. With this more stringent criterion, some subjects who would have been classified by other investigators as 'normotension' or white-coat hypertension are classified by us as masked hypertension or sustained hypertension respectively. Despite this, our data clearly demonstrated a higher prevalence of endorgan damage in masked hypertension and sustained hypertension.

Conclusion

Our cross-sectional association study supports the performance of ABP measurements^{32,33} in persons with type 2 diabetes. This strategy enables detection of masked hypertension in those with normal CBP, and differentiates white-coat from sustained hypertension. Masked hypertension, which has a prevalence of 18% among those with normal CBP, is associated with a higher prevalence of urinary albumin excretion, left ventricular diastolic dysfunction, and left ventricular hypertrophy. White-coat hypertension, which accounts for 55% of those with high CBP, carries a more benign prognosis than sustained hypertension and masked hypertension.

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