Clinical Application of a Complex of Blood Pressure Profile, Arterial Stiffness and Albuminuria for Cardiorenal Risk Assessment in Diabetic Patients

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Abstract: Background: In modern epidemiology, risk assessment is a crucial step in diabetes care. Clinic blood pressure reading though is not a good measurement for this purpose since both uncontrolled hypertension and white coat hypertension (WCH) are frequent among patients with diabetes mellitus (DM). Given the problems with clinical application of ambulatory blood pressure monitoring (ABPM), in this study we evaluated clinical utility of home self measurement (HSM) with a wrist-cuff device in DM patients with hypertension to make a BP profile. Also, the clinical application of a complex of arterial study, albuminuria and blood pressure profile, in DM risk assessment was investigated. Methods and Materials: Seventy-eight adult DM patients with labile or uncontrolled hypertension were randomly assigned to 24 hour ABPM or HSM for 4 consecutive days and their BP profiles were evaluated in conjunction with an assessment of arterial stiffness and renal function as well as lipid profile. Results: The two groups were of comparable age, gender, BP, DM duration and control, smoking, lipids, renal function, arterial compliance and antihypertensive medication use. ABPM detected 33% WCH and 17.6% evening/night-time dipping, compared to 32% and 16% respectively for HSM, with overlapping 95% confidence intervals for day versus night BP regression coefficients. WCH patients had more compliant arteries as well as less albuminuria compared to the sustained hypertensive group. Conclusion: A complex of BP profile (by either ABPM or HSM), arterial compliance and albuminuria is a reliable and economical alternative to current methods for risk assessment in hypertensive diabetic patients.

Keywords: Blood pressure monitoring, diabetes, arterial compliance, microalbuminuria.

INTRODUCTION

Hypertension is common in Diabetes Mellitus (DM) with 71-93% of diabetic patients being hypertensive [1]. Unfortunately blood pressure (BP) control is more difficult in DM. A large study reported that while more than 63% of DM patients needed more than one antihypertensive medication, BP control was achieved in only 18%, markedly lower than the non-DM group [2]. Hypertension detection and control is therefore of paramount importance in this population and yet clinic BP measurement is often unreliable with a substantial number of patients having WCH and probably misclassified [3] as poorly controlled. More importantly, the pattern of BP fluctuations can lead to a better risk assessment of patients with diabetes, chronic kidney disease and cardiovascular diseases. For instance, non-dipping nocturnal BP is now established as a CV early risk marker and associated with target organ damage, even in healthy normotensive population [4, 5].

Ambulatory blood pressure monitoring (ABPM) is the gold standard for WCH diagnosis [3, 6]. Furthermore, it measures night-time BP, illustrates BP and heart rate variability and can indirectly assess arterial compliance [7, 8]. Consequently, it is superior to clinic BP in predicting cardiovascular events and all-cause mortality [9-11]. Moreover, in PAMELA study it had a better prognostic value for all-cause mortality when compared to other methods of BP measurements in a general population over 11 years of follow-up. However, ABPM is frequently accompanied by patient discomfort and intolerance, particularly if repeated, and because of its expense it is not widely available in clinical practice. Instead, home-self measurement (HSM) is now a popular alternative being more convenient, significantly cheaper and also suitable for patient follow-up [12]. It is also a more robust predictor of cardiovascular and all-cause mortality than clinic BP [10]. While arm-cuff devices have usually been used for HSM, wrist-cuff devices are now commonly used by patients because of ease of use, particularly in the elderly, the handicapped and those with large upper arms [13]. However, despite these advantages, most wrist-cuff devices are not recommended by the British and European societies of hypertension [14, 15] and the issue of arm position is still debated [16, 17].

The aim of this study was firstly evaluating BP profile by either ABPM (with an automated device) or HSM (using a validated wrist-cuff monitor) for risk assessment in patients...
with DM to investigate the potential substitution of simple measurement for a complicated procedure. In addition, association between aortic pulse wave velocity and pulse wave analysis as surrogated of arterial stiffness, albuminuria and white coat condition was investigated to evaluate their potential clinical application for the risk assessment in DM subjects in conjunction with BP profile.

**MATeRIAls AND Methods**

**Subjects**

Ninety consecutive outpatient adult DM patients with labile or uncontrolled hypertension entered to the study. They were randomly assigned to 24 hour ABPM or HSM for 4 consecutive days (60 and 30 persons respectively) and their BP profiles were evaluated in conjunction with an assessment of arterial stiffness and renal function as well as lipid profile. However, 78 patients (86.6%) complied with the instructions including 52 and 26 individuals in ABPM and HSM groups respectively.

The study subjects consisted of 78 adult DM patients with labile or uncontrolled BP attending an outpatient diabetic clinic. Patients with atrial fibrillation, severe heart disease, renal transplant, end-stage renal disease, severe renovascular disease, primary hyperaldosteronism, pheochromocytoma, and pregnant women were excluded. Each participant provided informed consent for the study, which was approved by the Human Research Ethics Committee, The University of Newcastle and the Hunter-New England Health Ethics Committee (NSW, Australia). In this selected DM population, 82% had type 2 DM, mean age was 61 y., 51% were male and 13% smokers (Table 1). Twenty-five percent had a history of ischemic heart disease, 13% a previous cerebrovascular event, 8% peripheral vascular disease and 72% were hyperlipidemic or taking lipid lowering medication. Sixty four percent were taking more than 1 medication for BP, which included 47% angiotensin receptor blockers, 46% ACE inhibitors, 43% diuretics, 39% beta blockers, 38% calcium channel blockers, 10% alpha-blockers and 4% vasodilators. In respect to diabetes medication, 47% of the individuals were taking a biguanide, 15% a sulphonylurea, 4% from other oral hypoglycemic agents; and 53% on insulin. Forty two percent were taking aspirin, 11% occasionally used non-steroidal anti-inflammatory drugs and 4% were on anti-coagulant agents.

**Measurements**

Participants were randomly allocated to an automated 24 hour ABPM (Spacelabs 90219) or 4 consecutive days of a validated oscillometric wrist-cuff HSM device (Omron HEM-609). Two-third of subjects was allocated to ABPM (i.e. 52 ABPM and 26 HSM) since it is currently the preferred option by clinical practice guidelines from related authorities [3, 18-21]. BP was measured every 20 minutes during the day and every hour at night with ABPM. HSM included five measurements at approximately 0800, 1200, 1600, 1800 and before going to bed, during each of the 4 consecutive days and the recorded patients’ logs were compared to the devices inbuilt memory for measurement validation. All patients were informed about monitor use including correct arm position and were provided with instructions.

In order to calibrate HSM (group A) with ABPM (group B), the day time was assumed to be from 0600 to 1800 and evening/night time from 1800 to 0600 hrs. The criteria for WCH diagnosis was ambulatory average daytime BP≤135/85 mmHg despite a hypertensive state as measured in clinic or office [3, 20]. Although HSM did not include sleeping BP, the average of two evening BP measurements in the period of monitoring was used as a surrogate for nighttime BP in the group A, because European Society of Hypertension clearly suggested that nocturnal hypertension may be suspected on the basis of increased evening home blood pressure [3]. Nocturnal dipping was calculated as (mean daytime BP – mean nighttime BP)/ mean daytime BP] and patients with less than 10% SBP dipping were identified as non-dippers [3, 22]. Also the absolute white coat effect and nighttime BP reduction were considered in the analysis. As stated in PAMELA study the day to night time ratio was applied as a marker of BP pattern [10].

Arterial compliance was measured by pulse wave velocity (Complior®, Colson, Paris, France) and Pulse Wave analysis (SphygmoCor®, AtCor Medical, Sydney, New South Wales, Australia) and pulse pressure was considered as an indirect measure [23]. Pulse wave velocity (PWV) measurement involved the placement of sensors over the carotid and femoral arteries, the carotid-femoral (CF) velocity being an index of central arterial stiffness [24]. Pulse wave analysis was measured using a sensor on the radial artery, resulting in the measurements of augmentation index (Alx), adjusted for heart rate, ejection duration (ED), the time of the reflected wave (rTr) as well as peripheral and aortic pulse pressure (PP). Estimation of cardiovascular risk

| Table 1. Patients’ Characteristics in the BP Monitoring Groups, all P Values >0.05 |
|---------------------------------|----------|----------|----|
| Age (y) | 61.7 (1.5) | 60.6 (2.4) | 0.71 |
| Male (%) | 53 | 46 | 0.81 |
| Smoker (%) | 14 | 12 | 1.00 |
| DM duration (y.) | 11.3 (1.7) | 10.4 (1.7) | 0.73 |
| HbA1c (%) | 7.5 (0.2) | 7.5 (0.9) | 0.43 |
| Cholesterol (mmol/l) | 4.7 (0.1) | 4.4 (0.2) | 0.17 |
| Triglyceride (mmol/l) | 1.8 (0.1) | 1.8 (0.1) | 0.21 |
| eGFR (MDRD)ml/min/1.73 m² | 74.6 (3.3) | 77.4 (4.2) | 0.61 |
| Clinic SBP (mmHg) | 148.0 (2.6) | 148.0 (3.4) | 0.95 |
| Clinic DBP (mmHg) | 82.9 (1.8) | 79.6 (2.1) | 0.27 |
| Clinic Heart Rate (bpm) | 70.9 (2.3) | 71.9 (2.5) | 0.78 |
| 5 year estimated CV risk (%) | 45 (2) | 42 (2) | 0.44 |
| Adjusted Alx (%) | 22.7 (1.7) | 24.2 (0.7) | 0.53 |
| CF-PWV (m/s) | 12.2 (0.4) | 12.4 (0.7) | 0.78 |
| Average number of anti-HT meds | 2.3 (0.2) | 2.2 (0.3) | 0.70 |

Values are the means (SEM) unless specified; SBP: systolic blood pressure, DBP: diastolic blood pressure, Alx: augmentation index, CF: carotid-femoral, PWV: pulse wave velocity
was based on 11 risk factors to quantify an adult’s risk of death from cardiovascular disease, including stroke and coronary heart disease, as calculated by the “Risk Score Calculator” (www.riskscore.org.uk). Kidney function was assessed by MDRD formula (eGFR) (http://nephron.com/cgi-bin/MDRD_NKF.cgi).

Analysis

For validation purposes, ABPM was considered as the gold standard. The ABPM group was double the HSM group in sample size which increased the power of the study analyses. The two groups were compared by t-test for normally distributed variables and Mann-Whitney U test were applied for non-normally distributed ones. The proportion of the nominal variables was compared by Chi² between the two groups. Regression coefficient of the day versus night natural logarithm of BP (as an index for BP night-dipping) was calculated with 95% confidence interval (CI), separately for SBP and DBP and for both BP monitoring methods in order to know whether this association is consistent and comparable between the two methods of BP monitoring. The power of tests for desired detectable level for BP, as much as 2 to 5 mmHg was 91 to 99% and also 0.5 m/s difference in PWV. P value was considered significant if it was less than 0.05 for all tests. Correlation of the continuous variables was carried out by Spearman method. SPSS-12 software was applied for analyses.

RESULTS

BP Profile

The HSM and ABPM groups were comparable regarding their age, gender, DM duration, clinic BP, arterial compliance, glycemic control, renal function and lipid profile as well as estimated 5-year cardiovascular risk score (Table 1). There was no significant difference in the medication use between the two groups except insulin use which was more frequent in the HSM group (79% compared to 42%).

The BP monitoring results demonstrated that 33% of all subjects had WCH, 83% were non-dippers for SBP and 71% non-dippers for DBP. Interestingly, the recorded mean SBP and DBP as well as the daytime and evening/nighttime SBP and DBP by HSM and ABPM were comparable. Moreover, there was no significant difference between the two methods in detecting WCH and the non-dipper conditions (P>0.05) (Table 2).

![Fig. (1). Day (D) against night (N) blood pressure (mmHg) for systolic (SBP) (left) and diastolic (DBP) (right) measurements by ambulatory blood pressure monitoring (ABPM-solid line) and home self-measurement (HSM- dashed line). The figure demonstrates that, HSM overestimates NSBP in high levels of SBP, however the difference is minimal when compared to ABPM. For DBP, disagreement is more prominent in lower levels of BP, with HSM overestimating NDBP. However the difference is minimal in usual levels of BP.](image-url)

<table>
<thead>
<tr>
<th>Table 2. BP Monitoring Results</th>
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<tbody>
<tr>
<td>ABPM</td>
</tr>
<tr>
<td>24-hr</td>
</tr>
<tr>
<td>138.6 (2.4)</td>
</tr>
<tr>
<td>77.1 (1.6)</td>
</tr>
<tr>
<td>Day-time (0600-1800)</td>
</tr>
<tr>
<td>140.6 (2.4)</td>
</tr>
<tr>
<td>79.1 (1.6)</td>
</tr>
<tr>
<td>Night/Evening-time</td>
</tr>
<tr>
<td>135.4 (2.5)</td>
</tr>
<tr>
<td>72.8 (1.6)</td>
</tr>
<tr>
<td>White-Coat Hypertension diagnosis (%)</td>
</tr>
<tr>
<td>33</td>
</tr>
</tbody>
</table>

Values are the means (SEM) unless specified.
Comparison of the sustained or ambulatory hypertensive (AH) and WCH patients revealed that DM duration, glycemic control, cholesterol and eGFR were not significantly different between these two categories. In contrast, CF-PWV was significantly lower in WCH subjects (P=0.03 by t-test and p=0.01 by Mann-Whitney U), despite AxI being comparable between the two groups. Likewise no statistical significant difference was detected between the two groups regarding ED and rTr. While peripheral and aortic PP were comparable between the two groups, ambulatory day and night time PPs were significantly lower for WCH than within the sustained hypertensive group (P<0.0001). In addition, patients with WCH had less albuminuria (P=0.02) (Table 4, Fig. 2).

No relationship was detected between WCH or non-dipper conditions and DM duration, gender, history of cardiovascular disease and hyperlipidemia.

**Table 4. Vascular Indices for Patients with Sustained Hypertension and White-Coat Hypertension**

<table>
<thead>
<tr>
<th>Metric</th>
<th>AH N=52</th>
<th>WCH N=26</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes duration (months)</td>
<td>120 (36-201)</td>
<td>84 (5-156)</td>
<td>0.18</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 (6.6-8.4)</td>
<td>7.3 (6.6-8.2)</td>
<td>0.98</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.7 (3.9-5.1)</td>
<td>4.6 (3.8-5.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>eGFR (MDRD) ml/min/1.73 m2</td>
<td>73.6 (63.3-88.8)</td>
<td>76.6 (56.6-88.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Albumin Creatinine Ratio (mg/mmol)</td>
<td>1.8 (1.1-3.5)</td>
<td>0.7 (0.3-2.4) #</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted AxI (%)</td>
<td>25.0 (17.5-30.5)</td>
<td>24.0 (19.2-29.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>CF-PWV (m/s)</td>
<td>12.4 (11.1-14.1)</td>
<td>10.2 (9.3-12.3) *</td>
<td>0.01</td>
</tr>
<tr>
<td>Peripheral PP (mmHg)</td>
<td>68.0 (56.7-82.0)</td>
<td>59.5 (48.0-75.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Aortic PP (mmHg)</td>
<td>51.0 (38.0-69.0)</td>
<td>48.5 (35.0-54.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Ambulatory Day pulse pressure</td>
<td>68.0 (62.5 - 74.0)</td>
<td>53.0 (46.0 - 59.0) §</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ambulatory Night PP</td>
<td>69.0 (62.0 - 76.0)</td>
<td>56.0 (43.2 - 61.7) §</td>
<td>0.0001</td>
</tr>
<tr>
<td>Non-dipper SBP (%)</td>
<td>78.8%</td>
<td>80.2%</td>
<td>0.87</td>
</tr>
<tr>
<td>ED (%)</td>
<td>35 (31-38)</td>
<td>33.5 (31.0-38.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>rTr (ms)</td>
<td>0.154 (0.135-0.185)</td>
<td>0.151 (0.133-0.178)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Values are median (inter-quartile range) unless specified; AxI: augmentation index, CF: carotid-femoral, PWV: pulse wave velocity, ED: Ejection duration, rTr: relative time for reflected wave return

# P=0.02, * P=0.01, § P=0.0001; all non parametric tests

**DISCUSSION**

In this study approximately 32% of DM clinic patients with poorly controlled hypertension diagnosed at a diabet ic clinic had WCH and only 17% of the patients had a significant evening/night dipping SBP. Of particular importance a four day HSM with 3 daytime and 2 evening time readings was practically as useful as 24 hour ABPM in detecting WCH and non-dipper conditions. It was also revealed that patients with WCH had better arterial compliance and less albuminuria than those with sustained hypertension.

The utility of HSM as an alternative to ABPM in the detection of WCH has long been an issue. However Stergiou et al have shown that HSM can be used for WCH diagnosis [25] and it has recently been accepted for screening of WCH, although the diagnosis should be confirmed by ABPM [26, 27]. Nevertheless, BP measurement guidelines from the British and the European hypertension societies [15, 28, 29] do not support using devices that measure BP in the finger or in the arm below the elbow until they are validated according to international protocols. Therefore, we applied a validated device for this purpose. However the number of reports demonstrating the validity of wrist-cuff monitors is increasing [30-35], though with particular considerations including wrist position[16]. Furthermore, in a recent study a wrist monitor was comparable to an automated upper arm device and closer to the mercury sphygmomanometer [32] and in another, the result of the wrist monitor was closer to the intra-arterial BP than a mercury device [30]. In this study we used a popular wrist-cuff BP monitor [17, 35] which has been validated and described by patients as convenient and easy to use. In order to compare non-dipping detection with HSM and ABPM, night-time blood pressure was considered to be after 1800, and while this is not the usual ABPM time, a similar time has been applied during another DM study...
In that study, Masding et al. compared average BP readings at 1300 and 2300 by HSM over 3 days in 55 diabetic patients and considered a BP fall of 20/10 mmHg as a criterion for night-dippers. They concluded that this approach despite its sensitivity, was not specific enough to detect the non-dipping condition, although was far superior to clinic BP in the detection of true hypertension. Using a wrist-cuff monitor and different criteria for night-dipping diagnosis, our results suggest that the average evening BP reduction measured by HSM, may predict BP dipping during sleep.

Previous reports on the frequency of WCH in DM widely vary from 23 to 62% for type 2 and 68 to 75% for type 1 DM [37-42]. However, this variation is partially due to definition differences. For instance Burgess et al., who reported a prevalence of 62% WCH in DM, identified WCH as mean day BP< mean clinic BP. Applying this description in our study would result in a 71% prevalence of WCH.

The relationship between ABPM findings and diabetes complications including nephropathy has scarcely been reported [37, 43-45]. Nielsen et al. also reported 23% WCH in diabetic patients with normoalbuminuria, 8% in microalbuminuria and 9% in nephropathy [38], which is in agreement with our findings. The greater likelihood of albuminuria in sustained hypertensive patients when compared to WCH reflects the severity of general vascular damage in this population and is consistent with the increased CF-PWV in the sustained hypertensive group [46]. While reduced CF-PWV and therefore arterial stiffness noted in DM patients with WCH has not been previously reported, it is consistent with a report in non-DM patients [47]. Given PP as an indirect measure of arterial stiffness, it was interesting that neither peripheral nor aortic PP was different between sustained hypertensives and WCH, but ambulatory day and night PP were significantly lower in WCH. This is in line with some other reports of a greater predictivity of ambulatory obtained BP profile for mortality risk [48].

The above evidence suggests that in the presence of albuminuria and increased arterial stiffness, WCH would be less likely and therefore clinic BP is more likely to represent the real BP. Also, PP is not a valid marker of arterial stiffness unless the PP estimation is based on ambulatory BP measurement.

While 83% of our study population were non-dippers, compared with 30 to 64% in other studies [42, 45, 49], the greater frequency of non-dipper in our study is probably...
related to our selection criteria, since only patients with labile or uncontrolled hypertension were selected. We did not find any relationship between non-dipping condition and DM duration, HbA1c and microalbuminuria, which supports previous studies. Nevertheless, non-dipping is now a proven risk for all-cause and cardiovascular mortality [4, 50] and vascular events [45] in DM. Considering that the short-term reproducibility of the non-dipping pattern in DM patients is better than in non-DM hypertensive patient [49], BP monitoring may provide an opportunity for a better risk assessment in DM patients. However, consideration of a cut-point rather than using a continuous value in the BP dipping definition is criticized by some authors [22].

Finally, the current study, enhances the previous evidence of the role of arterial assessment in risk assessment and better management of CVD, particularly in DM [51].

In conclusion, HSM using a validated wrist-cuff monitor is as useful as ABPM in identifying DM patients with WCH in this population. Furthermore, HSM can be used to detect nocturnal non-dipping BP in such individuals. Of particular interest, it was observed that DM patients with WCH manifest more compliant arteries and less albuminuria when compared to DM individuals with sustained hypertension. This provides a battery for easy renal-cardiac risk assessment in DM population.

ACKNOWLEDGEMENT

The Authors would like to acknowledge the support of Dr. J. Lowe, Dr. T. Donnelly, Dr. S. Linjawi and Dr. E. Tyson as well as Hunter New England Health Services and Diabetes Education Centers.

CONFLICTS OF INTEREST

None declared.

Appendix

Summary

‘What is known about topic’
- White-coat hypertension (WCH) is a common finding in diabetes mellitus
- While automatic ambulatory blood pressure monitoring (ABPM) is the gold standard for the WCH, it is often not very convenient, unrepeatable, expensive and unavailable in practice
- Home self BP measurement (HSM), in particular with popular wrist-cuff devices, is more convenient, repeatable and cheaper, but must be validated in the target groups

‘What this study adds’
- HSM with a wrist-cuff device had comparable BP profile result with ABPM in two comparable groups with diabetes and hypertension
- Average evening BP measured by HSM may predict BP dipping during night
- Patients with WCH had less central arterial stiffness (as measured by CF-PWV and ambulatory PP) and albuminuria than the sustained hypertensive group. Therefore these markers may predict the likelihood of WCH in clinical practice

REFERENCES

Diabetes Risk Assessment


