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BLOOD PRESSURE VARIABILITY AND RISK FOR PROGRESSION OF CARDIOVASCULAR AND RENAL DISEASES IN PATIENTS WITH DIABETES MELLITUS

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Abstract

Accurate measurement of blood pressure (BP) and evaluation of global cardiovascular risk is crucial for diagnosis and treatment of hypertensive patients. When hypertension and diabetes mellitus are associated, the risk for cardiovascular events is bigger than the sum of the components. Beyond systolic and diastolic BP values as targets for antihypertensive treatment, recent guidelines recognize BP variability as an independent predictor for future cardiovascular events. 24 hours ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) are two methods used in patient day to day life conditions for BP measurements. Increased variability of systolic and/or diastolic BP within one day ("short-term BP variability") and also over longer periods ("long-term BP variability") showed by ABPM and/or HBPM is associated with target-organ damage and cardiovascular events. This review is focused on the prognostic importance of BP variability in hypertensive patients with diabetes mellitus.

key words: *blood pressure variability, hypertension, cardiovascular disease, diabetes mellitus*

Introduction

High blood pressure (BP) is the most common reason for visits to a physician in the United States [1] and remains in the top ten causes of death worldwide, with 1.1 million deaths in 2012, according to a Word Health Organization report [2]. Elevated BP is an important risk factor for cardiovascular events such as myocardial infarction, stroke or heart failure, which are the most frequent causes of death in people with kidney disease [1,3].

For a long period of time, American hypertension guidelines focused on systolic (SBP) and diastolic blood pressure (DBP) values as the only targets of treatment. In 2003, for the first time, the European guideline for the management of arterial hypertension introduced the concept of quantification of global cardiovascular risk in hypertensive patient,

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because the majority of the hypertensive population has additional cardiovascular risk factors, such as alterations in glucose and lipid metabolism. Moreover, when concomitantly present, hypertension and metabolic diseases lead to a global cardiovascular risk which is greater than the sum of its individual components [4].

On the other hand, type 2 diabetes mellitus (T2DM) itself is associated with very high risk of cardiovascular events, especially myocardial infarction. It was shown that diabetic patients without a previous myocardial infarction have a similar risk of myocardial infarction with that of nondiabetic patients with a previous myocardial infarction [5].

Diabetic patients have 2 to 3 times fold increased risk for developing hypertension as compared to non diabetic patients. When hypertension and diabetes coexist in the same patient, cardiovascular risk is significantly higher compared with nondiabetic individual [6].

Precise measurement of BP is important for the accurate diagnosis and management of hypertension. Isolated BP readings in doctor's office (office BP measure) cannot discover continuous BP changes in short or long–term periods of time. Other limitations of office BP include inaccuracy of the technique, "white coat effect" and operator dependence of the auscultator technique [3,7].

The aim of this article is to review the evidence from recent studies about BP variability as a prognostic factor for renal and cardiovascular outcomes in hypertensive patients with diabetes mellitus.

Diagnosis of BP variability

BP is characterized by important variability in healthy subjects within 24 hours, as an adaptative mechanism to emotional stimuli or physical activity. Increased BP variations within the 24 hours (over seconds, minutes and induced by circadian rhythm) is considered "short term BP variability". Variations in BP were also described over longer periods of time, between days, weeks, months, seasons or even years. This fluctuation of BP was named "long-term BP variability" [3,6].

In an attempt to overcome office BP measurement limitations, two techniques have been developed and used in the last decades for out-of-office BP measuring - 24 hours ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) (Table 1). These methods showed that BP measured in day to day life conditions could be a better risk predictor for cardiovascular events than office BP. Recordings from 24 h ABPM provide BP values during day and night. These BP recordings are used to calculate the standard deviation of systolic BP, diastolic BP and mean BP over the 24 hours (for a single day). This method allows exclusion of circadian BP variability. In particular, nocturnal BP levels are very important to know, because it has been shown to better predict cardiovascular events and mortality. Several studies have demonstrated that ABPM is better correlated with target-organ damage and cardiovascular events than office BP in diabetic patents. Similarly, by reflecting BP values over a few days, HBPM has been shown to better predict the major CV events, overall mortality and the progression of chronic kidney disease to end stage renal disease than office BP measurements [3].

Self measurements of BP by patient at home (home BP monitoring - HBPM) offer important findings in everyday life conditions, and detect short-term BP variability (over a single day) and long-term BP variability (between days, weeks, months) [8].

European [4] and American [9] guidelines recommend the use of ABPM and HBPM not as

a substitute, but as a complement to office BP measurement, for diagnostic and therapeutic decision and for relevant prognostic value, especially in treated hypertensive patients.

Table 1. Methods for measurement of BP in clinical practice (adapted after [7,8]).

Characteristics of BP measuring method	**Office BP**	**24 h ABPM**	**HBPM**
Availability	high	low	high
Cost	low	high	low
Number of readings	low	high	medium
Patient involvement	no	no	yes
Physician involvement	yes	yes	no
"White coat" effect	yes	no	no
Daytime BP	+	+++	++
Nighttime BP and dipping phenomenon	-	+++	±
24-hour BP variability	-	++	±
Long-term BP variability	-	±	++
Cause of BP variability	Salt intake Adherence to medication Anxiety because of visit (white coat hypertension)	Activity/inactivity Awake/asleep Drugs pharmacodynamics	Adherence to medication Other causes

HBPM by the patient should include 12 to 25 measurements in seven days, before each visit to physician's office, and one to two measurements per week during inter-vist period. HBPM might offer important information on BP control and increase patient's adherence to treatment [10].

The advantages of HBPM is sustained by a meta-analysis of 18 randomized controlled trials including people with essential hypertension, which showed that proportion of hypertensive patients achieving BP targets are increased with HBPM than office BP measurement [11].

The relevance of BP variability in clinical practice as an independent predictor for future cardiovascular events was recognized in 2011 in NICE guidelines for the management of hypertension [12].

Causes and mechanisms of BP variability

Hypertensive population. BP changes in the very short-term (ie. beat to beat) and in short-term (within 24 hours) reflect the influences of multiple factors, often intricated: central neural adaptative mechanisms (increased central sympathetic drive, reduced cardio-pulmonary reflex), humoral factors (insulin, angiotensin II, bradykinin, endothelin–I, and nitric oxide), rheological influences (blood viscosity), mechanical forces (ventilation) and behavioral factors (activity, sleep) [3]. Moreover, short-term and long-term BP variability may have contributors from both the patient (reduced adherence to low salt diet and/or medication) and the physician (inadequate dosing or drug class of antihypertensive medication) [3,8].

It is well known, but not proven by clinical trials, that patient's adherence to drug treatment is greater in clinical studies than in day to day clinical practice. Recent analyses of BP control degree correlated with cardiovascular outcomes from two clinical trials (INVEST and ONTARGET) suggested that patients with the highest percentage of visits to physician's office had the lowest cardiovascular event rates. Patients with lower adherence to antihypertensive drug treatment are younger, male sex and use of multiple drugs classes over

6 months [8]. It was shown that calcium–channel blockers and non-loop diuretics are effective for reducing BP variability, perhaps linked to better adherence [13].

Aditional mechanisms of BP variability in diabetic patients. Multiple factors (often intertwined) play an important role for the increased BP variability in diabetic patients, as shown in Figure 1.

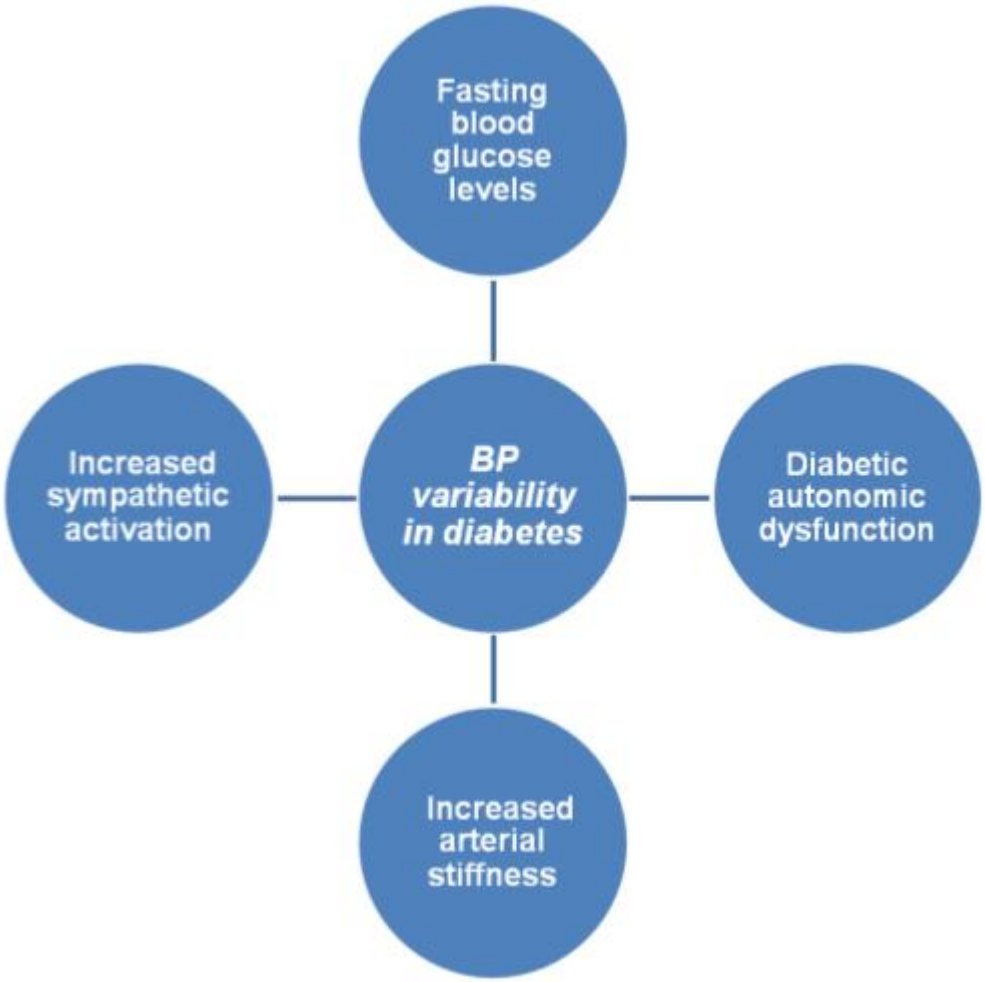

Figure 1. *Mechanisms of BP variability in diabetes (adapted from [3]).*

Prognostic importance of short-term BP variabilty

BP variability within 24 hours in the general population. Evidence from observational studies showed that in hypertensive patients an increased BP variability within the 24 hours is associated with the development, progression and severity of subclinical organ damage (ie. increased left ventricular mass index or carotid intima-media thickness) and with higher incidence of cardiovascular events and death [3,7]. Thus, increased BP variability is an independent and additional cardiovascular risk factor and is correlated with elevated mean BP levels. An increase in mean BP level is associated with increased BP variability [7].

Increased short–term BP variability (within 24 hours) is associated with increased risk of impaired glycemic control. In a recent large Japanese general population study, the prevalence of prediabetes and diabetes was significantly higher in hypertensive subjects with an increase of within- visit BP variability, independent of mean systolic BP [14].

BP variability within 24 hours in diabetic patients. On the other hand, in diabetic patients with hypertension, short-term BP variability (one day) has been found to be increased compared with hypertensive subjects without diabetes [15].

The role of increased BP variability as an additional cardiovascular risk factor in diabetic subjects is supported by the evidence that in diabetic patients with increased systolic BP variability the incidence of coronary artery disease is significantly greater compared with those without BP changes [16].

Prognostic relevance of long-term BP variability

Visit-to-visit BP variability exhibits BP changes over prolonged periods of time (days, weeks, months or even years). Long-term BP variability may have influences from short-term stressors (acute stimuli causing fear, excitement or pain) similar with 24 hours BP variability or reflect inadequacies of BP measurement technique by the physician or patient related poor BP control [3,17].

BP measurements performed by patients at home using HBPM are an adequate alternative to multiple BP measurements taken in the physician's office at spaced visits for the assessment of visit-to-visit BP variability [18].

Visit-to-visit BP variability in the general population. Similar with short-term BP variability, high changes of BP from visit-to-visit are associated with increased prevalence of cardiac (left ventricular diastolic dysfunction) [19,20], cerebral (increased white matter hyper-intensity volume, associated with impairment of cognitive function) [21] and renal (development of albuminuria) [22] subclinical organ damage in hypertensive patients.

The prognostic value of long-term BP variability for future cardiovascular events is supported by secondary analyses of several studies. Thus, the results of retrospective analyses of BP variability in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) published by Rothwell et al. showed that between visit systolic BP variability and episodic BP peaks (the maximum systolic BP) are strong predictors of stroke, independent of the mean BP [23]. Visit-to-visit BP variability was a stronger predictor of future transient ischemic attack and stroke than high mean systolic BP [23].

As well, increasing values of intra-individual visit-to-visit BP variability are associated with an elevated risk of coronary heart disease independently of mean office or ambulatory BP levels [24].

Several studies demonstrated the association between long-term BP variability and mortality. Analyzed data from the population based Third National Health and Nutrition Examination Survey (NHANES III) showed that higher visit-to-visit variability in systolic BP was associated with increased all-cause mortality in general population. Results from NHANES III showed an interesting sinusoidal relationship between BP variability and mortality. This particular relationship was present in individuals with a standard deviation of systolic BP higher than 8 mmHg who are at a 50% greater risk of death versus subjects with a standard deviation of systolic BP below 4.8 mmHg [25]. This surprising observation of Rothwell et al. allowed Poulter to postulate that episodic increased of BP levels with a relatively low mean systolic BP is associated with a higher risk of cardiovascular events than constant hypertension with higher mean systolic BP, but less BP variability [17].

A recent systematic meta-analysis of 37 studies showed modest associations between visit-to-visit BP variability with cardiovascular disease and all-cause mortality. For each 5 mm Hg increased systolic BP, the hazard ratio for stroke across 7 cohorts was 1.17 (95%

confidence interval [CI], 1.07-1.28), for coronary heart disease across 4 cohorts was 1.27 (95% CI, 1.07-1.51), for CVD mortality across 5 cohorts was 1.22 (95% CI, 1.09-1.35), and for all-cause mortality across 4 cohorts was 1.20 (95% CI, 1.05-1.36) [26].

Visit-to-visit BP variability in diabetic patients. In T2DM patients, visit-to-visit variability in systolic BP is directly correlated with increased degree of albuminuria (marker of development and progression of diabetic nephropathy) [27] and with pulse wave velocity and inversely correlated with ankle-brachial index as an indirect markers of atherosclerosis [28].

The importance of long-term BP variability as a predictor of microvascular complications in diabetes patients with hypertension was supported by several randomized controlled trials.

In a secondary analysis of the influence of increased BP and BP variability on the development of microvascular complications in type 1 diabetes patients included in the Diabetes Control and Complications Trial (DCCT), Kilpatrick et al reported that visit-to-visit BP variability predicts the risk for development of diabetic nephropathy, but not retinopathy [29].

In a recent post hoc analysis of IDNT (Irbesartan Diabetic Nephropathy Trial) and RENAAL (Reduction of End Points in Non-Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan) studies, the association between visit-to-visit systolic BP variability and kidney disease outcomes (time to doubling of serum creatinine level, end-stage renal disease or mortality) and cardiovascular outcomes (time to cardiac death, myocardial infarction, stroke, revascularization or hospitalization for heart failure) was examined in 2739 patients with T2DM and nephropathy. Secondary analysis of these two studies showed that increased systolic BP visit-to-visit variability is associated with a greater risk of the composite kidney outcome, and with end-stage renal disease, but not with the cardiovascular outcomes [30].

It was also shown that long-term BP variability is a predictor of future macrovascular complications (coronary events, stroke) in patients with diabetes. Thus, a post-hoc analysis of the ASCOT Trial (Anglo-Scandinavian Cardiac Outcomes Trial) database examined the relationship between coronary heart disease events and stroke events and three parameters of BP variability: within visit, 24-hour and "visit-to-visit" BP variability. Long-term ("visit-to-visit") BP variability was the best predictor for coronary and stroke events. In ASCOT subjects, increased BP variability was also associated with the presence of diabetes mellitus [17].

Long-term BP variability is also associated with increased mortality in diabetic patients. In a 5.5 year prospective study of 2161 patients with type 2 diabetes, visit-to-visit BP variability strongly predicted all-cause mortality, independent of mean BP [31].

Conclusions

Over the time, the challenge for practicing doctors is how to accurate measure blood pressure and, when it is high, to use the most effective and safest antihypertensive treatment to reduce cardiovascular disease and increase survival. Lowering of BP levels with antihypertensive drugs is effective in reducing cardiovascular morbidity and mortality, irrespective of the drug class used, but the residual cardiovascular risk is never lowered to the level of those who have "normal" BP without treatment.

For the accurate measurement of BP levels, recent international guidelines recommend the use of ABPM and HBPM, in addition to office

BP measurements. These two noninvasive BP monitoring techniques can identify the variations of BP levels over short-term (24 hours - ABPM) and long-term (days, weeks, months - HBPM) period.

Moreover, in diabetic patients, ABPM is important for detection of alterations in autonomic control of cardiovascular system in 24 hours: non-dipper pattern, increased BP variability and decrease heart rate variability. BP variability is an important risk factor for progression of target-organ damage and cardiovascular complications in hypertensive patients with diabetes. In the future more research is needed to evaluate the impact of the reducing of the increased BP variability (perhaps by increased patient's adherence to medication) on cardiovascular morbidity and survival.

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