Review

Should pulse pressure and day/night variations in blood pressure be seen as independent risk factors requiring correction or simply as markers to be taken into account when evaluating overall vascular risk?

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Abstract

Patients with a blunted fall in nocturnal BP (known as non-dippers) have a high risk of micro- and macrovascular complications, particularly if they have hypertension, but also in normotensive patients with diabetes. A blunted fall in nocturnal BP reflects the high level of CV risk in these patients. ABPM data indicating an altered circadian BP rhythm reverse circadian BP profile should alert the physician to the potential risk of complications and should lead to efforts to treat hypertension effectively, especially at night, and to check for sleep apnoea syndrome, particularly in cases of resistant hypertension, or autonomic neuropathy (postural hypotension), a well known risk factor for cardiovascular (CV) events. Patients should be carefully screened for nephropathy. However, the definitions of "non-dipper" vary widely. Suitable treatments are poorly defined, but angiotensin-converting enzyme inhibitors (ACEi), diuretics, salt restriction and the maintenance of continuous positive airway pressure (CPAP) can be used as non-specific treatments. The efficacy of taking blood pressure-lowering drugs at bedtime rather than in the morning is still debated but deserves attention. In the diabetic population, brachial pulse pressure (PP) is an independent predictor of cardiovascular mortality, but not of all-cause mortality. It is also associated with complications of both type 2 and type 1 diabetes, this effect being stronger for nocturnal than for diurnal PP, and is strongly predictive of coronary heart disease in patients with type 2 diabetes. The stronger association between PP and age in diabetic than in non-diabetic populations suggests that diabetes accelerates vascular ageing. In patients with incipient nephropathy or overt renal failure, PP increases CV risk. However, misinterpretation could be related to confusion between brachial PP and central PP. The therapeutic implications of PP measurement remain poorly documented in diabetes.

Résumé

Anomalies de la pression pulsée et des variations nycthémérales de la pression artérielle : facteurs de risque indépendants ou simples marqueurs ?

L’altération du cycle nycthéméral des pressions artérielles (PA), comme l’absence de chute des PA nocturnes (patients non dippers) augmente le risque de complications micro- et macrovasculaires chez les diabétiques normo ou hypertendus et les exposent à un excès de risque cardiovasculaire. Sa présence doit alerter le médecin et l’inciter à contrôler le plus efficacement possible les PA, et à dépister un syndrome d’apnées du sommeil d’autant plus volontiers dans ces cas d’hypertension résistante ou de neuropathie autonome. Une néphropathie doit être soigneusement documentée. La définition du phénomène non dipping varie cependant d’une étude à l’autre et mériterait d’être uniformisée. Seuls des traitements aspécifiques sont préconisés comme une restriction sodée, un appareillage pour apnées du sommeil ou encore l’emploi de certains diurétiques ou IEC sans qu’il soit pour l’instant montré qu’une réduction des pressions nocturnes se traduisse par une diminution de la morbi-mortalité. L’impact favorable d’une prescription au coucher plutôt qu’au matin d’un traitement antihypertenseur reste par ailleurs peu documentée chez le diabétique. La pression pulsée (PP), en général brachiale, est un facteur prédictif de mortalité cardiovasculaire, d’événements coronaires et de complications chez les diabétiques de type 1 et 2. Chez les patients insuffisants rénaux, une augmentation de la PP accroît le risque cardiovasculaire. L’association qui unit la PP à l’âge est le témoignage indirect d’un vieillissement vasculaire accéléré dans le diabète. La PP est en corrélation avec la
1. Introduction

Atherosclerosis is equally important for the development of stroke, coronary events, renal failure and dementia and is the main cause of isolated systolic hypertension involved in heart failure in the elderly. Great interest comes from the role of arterial stiffness in the development of cardiovascular disease. Unfortunately, the measurement of blood pressure with a cuff sphygmomanometer is inaccurate to estimate arterial stiffness and to detect early presence and progress of underlying diseases. Then, other markers are proposed to document cardiovascular risk and which may be predictors of cardiovascular events. Two components of blood pressure, night/day variations and pulse pressure (PP) are particularly studied in different populations. Circadian blood pressure depends on sympathetic activity, insulin resistance, but also on renal sodium excretion and various definitions of alteration of circadian profile are given. The circadian pattern of blood pressure, established by 24-hour BP monitoring, varies between patients and in specific groups, its alteration could be associated with CV events. The other component, PP, is a very complex parameter to analyse for clinicians, as pathophysiological aspects, definitions (brachial or central) and methods of measurement are sometimes difficult to understand, but it has recently focused attention on the fact that drugs for hypertension act differently on central PP when no difference for SBP or brachial PP was found [1]. An increased of arterial stiffness could be involved in the loss of nocturnal decline of BP. We speculate that arterial stiffness could be one of the pathophysiological link between night/day variations of BP and PP, as in treated hypertensive patients on hemodialysis, arterial distensibility and nychthemeral BP impairment are possibly linked [2]. We successively review clinical applications of these two potential actors of CV risk.

2. Is blood pressure variability a cardiovascular risk factor?

2.1. Definitions

Increases in the absolute values of systolic and diastolic BP are clearly associated with CV disease. BP generally falls by at least 10% during the night in normal subjects (“dippers”). In some patients (“non-dippers”), there is a loss of nocturnal decline in BP. A third category of patients, “extreme dippers” has also been defined, in which BP falls by more than 20% overnight. However, these subjects are generally considered together with dippers. A final category, “reverse dippers”, is defined by an increase in systolic BP during the night. This pattern is sometimes analyzed separately in older populations. The prevalence of non-dippers has been estimated at about 41 to 60% [3,4].

2.2. Studies in the general population

2.2.1. Cardiovascular risk

Ambulatory BP variations seemed to be more closely associated with CV events than casual BP measurements in patients with essential hypertension [5]. In the Ohasama study, nocturnal blood pressure was found to be significantly more predictive of cardiovascular mortality risk than diurnal blood pressure during 10.8 years of follow-up [6]. Small day-night differences in BP have been shown to be associated with a higher risk of hypertensive CV complications and target organ damage (left ventricular changes or funduscopic changes) was found in patients with high nocturnal diastolic BP [7]. The prevalence of the non-dipping profile was significantly higher in patients considered to have a high CV risk (42%) than in those with a medium (33%) or low (29%) risk [8]. Some controversy remains concerning the possible association between blunted nocturnal decrease in BP and left ventricular mass: this association has been observed in elderly patients with systolic hypertension and in never-treated hypertensive patients with a persistent non-dipper pattern [9,10]. In treated hypertensive patients, cardiac structure is not affected by dipping pattern [11]. It has also been suggested that endothelial function is impaired in hypertensive patients with a non-dipper profile [12]. Non-dippers have been shown to have lower levels of endothelium-dependent vasodilation than dippers, due to lower levels of NO release. A low dose of aspirin (100 mg a day), inducing the NO release, administered at bed time, has been shown to reduce BP specifically in patients with untreated mild hypertension [13].

2.2.2. Stroke

The risk of stroke has been directly linked to the degree of hypertension. Following acute ischemic or hemorrhagic stroke, the decrease in nocturnal BP was found to be blunted in 88% of the patients [14]. The non-dipping profile has been associated with an increase in silent vascular damage in the elderly [15]. In the Ohashama study, no consistent association was observed between dipping pattern and the total risk of stroke, but the cerebral infarction risk was significantly higher in subjects with a < 10% nocturnal decline in BP (non-dippers and reverse dippers) than in patients with a nocturnal BP decrease of at least 10% (dippers and extreme dippers) (RH = 1.59 (95%
gastric) in both hypertensive and normotensive patients, dipper or not [16].

2.2.3. Renal failure

A lack of decrease in nocturnal BP has been reported in kidney failure requiring haemodialysis [18]. In treated hypertensive haemodialysis patients, nocturnal BP is an independent predictor of CV mortality, with a relative risk of 1.41 (95% CI: 1.08-1.84; \( P = 0.01 \)) [18]. In a three-year longitudinal study, the rate of creatinine clearance was found to decrease more rapidly in non-dippers than in dippers (0.37 ± 0.26 vs 0.27 ± 0.09 ml/min/month; \( P = 0.002 \)) [19]. Subjects with essential hypertension and microalbuminuria displayed no decrease in nocturnal blood pressure and median levels of urinary albumin excretion (UAE) were higher in non-dippers than in dippers [20,21]. The circadian rhythm of UAE was disturbed in non-dippers. Essential hypertension and renal sodium handling may be involved in this disturbance: effects on glomerular capillary pressure in situations of high sodium intake may result in a nocturnal fall in arterial sodium excretion in dippers, but not in non-dippers, and a larger decrease in UAE in dippers than in non-dippers [22]. Interestingly, the administration of valsartan before bedtime rather than in the morning improved the diurnal/nocturnal BP ratio to give a more dipper-like profile (75% of non-dippers became dippers). Three months of such treatment also significantly decreased urinary albumin excretion independently of decreases in 24-hour blood pressure [23]. Furthermore, enhanced sodium sensitivity was identified as an independent determinant of blunted nocturnal decrease in BP in essential hypertension and sodium restriction restored the dipper pattern. A decrease in renal sodium excretory capacity may therefore be one of the mechanisms involved in non-dipping behaviour [24]. Diuretics also shifted the circadian rhythm of BP from a non-dipper to a dipper profile in patients with essential hypertension, providing further evidence that sodium metabolism may be involved in generating the dipping pattern [25].

2.2.4. Obstructive sleep apnoea

More than 60% of patients with obstructive sleep apnoea are non-dippers [26]. Nocturnal BP variability has been shown to be related to the severity of the syndrome and to the apnoea-hypopnoea index, and to be independent of obesity [26]. The use of a nasal CPAP device restored the normal circadian dipper pattern: systolic and diastolic nocturnal (but not diurnal) BP decreased significantly after only two to four days of treatment, and the percentage of non-dippers fell from 79% before treatment to 50% after treatment [27,28].

2.3. Studies in patients with diabetes

In a population-based cohort of 70-year-old men (n = 1057), diabetes was more common in non-dippers (26%) than in dippers (14%; \( P < 0.05 \)) [3]. Small or non-existent decreases in nocturnal BP were encountered in about 30% of the normotensive or hypertensive type 2 diabetic patients [29,30]. Non-dippers were generally older than dippers [31]. During an average follow-up period of four years, a reversed circadian BP rhythm in hypertensive patients with type 2 diabetes was associated with the occurrence of vascular events (renal failure requiring dialysis, congestive heart failure, angina pectoris, acute myocardial infarction, cerebral infarction, diabetic gangrene and vitreous haemorrhage), with a statistically significant adjusted relative risk of 10.6 for fatal events (1.6-72.7; \( P = 0.014 \)) and of 4.1 for non-fatal events (1.7-10.2; \( P = 0.002 \)) [30]. In a four-year retrospective study, the mortality rate was 26% in non-dippers and 8% in dippers, due to the older age, a longer duration of diabetes and the presence of renal impairment in non-dippers [31]. Mean 24-hour systolic BP and diastolic BP were higher in non-dippers than in dippers and macro- and microvascular complications were more common in non-dippers than in dippers [32,33]. In patients with type 1 diabetes, a blunted nocturnal decrease in BP was associated with retinopathy [34]. In normotensive patients with type 2 diabetes, reversed circadian BP rhythm was associated with overt nephropathy, but not with retinopathy [33]. Non-dipping is correlated with UAE in patients with type 2 diabetes and has been observed in 80% of patients with macroalbuminuria, 74% of patients with microalbuminuria and 43% of patients with normoalbuminuria [35]. In type 1 diabetic adolescents, the risk of progression to microalbuminuria was 70% lower in those whose BP during sleep decreased normally [36]. Creatinine clearance decreased by 2.9 ml/min/year in dippers and by 7.9 ml/min/year in non-dippers (\( P < 0.05 \)) in a small retrospective study on diabetic patients with hypertension [37]. Autonomic neuropathy was found to be associated with UAE and blunted nocturnal decreases in BP in patients with type 1 or type 2 diabetes; this condition may contribute to the higher level of CV morbidity and mortality in this population [38-40]. This association between autonomic dysfunction and UAE rate is encountered even before the development of renal disease, as sympathetic activity is associated with a blunted fall in nocturnal BP in normoalbuminuric normotensive adolescents or adults with type 1 diabetes [41,42].

Insulin resistance has been associated with blunted diurnal BP variation, after adjustment for body mass index, fasting glucose level and mean 24-hour systolic BP (adjusted odd ratio of 6.2, 2.4-17.1; \( P = 0.0002 \)), very early in diabetes, before the occurrence of hyperglycaemia or hypertension, suggesting that metabolic abnormalities rather than circadian BP pattern alone may contribute to CV complications [43].
may thus be a close relationship between insulin resistance, sympathetic activation, which increases, and hypertension [44].

3. The limitations of circadian BP profile as a surrogate marker of CV events

Problems of definition: the definitions of "dipping" based on diurnal and nocturnal BP vary considerably, and at least five definitions having been recorded [45]. For example, nocturnal dipping has been defined as a greater than 10% reduction in the average systolic BP and diastolic BP at night compared with the daytime values [46] or if the nocturnal decrease in systolic BP only is >10% [4]. The nocturnal diastolic BP decline > 10% of daytime values has been also considered [19]. The reproducibility of ABPM also remains a matter of debate [47]. There is a high risk of false-positive or false-negative results if only one 24-hour recording is used: when BP was monitored over 48 hours, 28% of the dippers on day 1 were non-dippers on day 2 and 31% of the non-dippers on day 1 were dippers on day 2 [46]. The reproducibility of circadian systolic BP variation was found to be so poor in the elderly (with a coefficient of variation >130% and 36-43% of the patients changing dipping status) that the authors of the study concerned recommended that the notion of "dipping" should be abandoned in this population [48]. However, the classification of diabetic hypertensive patients as dippers or non-dippers on the basis of a single ABPM was more reliable than that in non-diabetic patients: 58% remained non-dippers, 31% remained dippers and only 11% of the patients had a variable dipping pattern when 2 ABPM recordings were taken [49].

Problems of reliability: several confounding factors may affect the relationship between blunted nocturnal decreases in BP and the occurrence of complications. Both sleep quality and the degree of activity in the morning have been found to be associated with poor reproducibility for nocturnal decreases in BP [50]. Patients with a non-dipping profile usually have a higher mean 24-hour BP, which may itself lead to complications. Mean age (non-dippers are older than dippers), diabetes duration and antihypertensive therapy are also potential confounding factors (particularly if the occurrence of microvascular complications is analyzed).

Problems of the population studied: if an epidemiological relationship between circadian variation of BP and CV risk has been established, the prognostic significance of a blunted fall in BP is less clear at an individual level. After having taken into account confounding factors, the value of a loss of circadian blood pressure is probably useful as a surrogate marker of cardiovascular risk and target organ damage.

Problems of treatment: Few studies have focused on the impact of treatment. As already said, salt restriction, the use of ACEi, diuretics, or perhaps a low dose of aspirin given at bedtime, or the treatment of apnoea syndrome, could all potentially improve prognosis, possibly by decreasing nocturnal BP. For example, in a small pilot study, trandolapril treatment for two weeks restored a normal circadian profile [51]. The potential reduction of CV risk through the normalisation of circadian variations in blood pressure has not been assessed in detail: in the HOPE study, the authors suggested a possible improvement in CV outcome following the administration of ramipril at bedtime, and an increase in diurnal/nocturnal BP ratio [52]. But the critical point is that no study has clearly demonstrated that a better “nocturnal dipping profile” restored by drugs improve cardiovascular mortality and/or morbidity.

Problems of reimbursement: In France, ABPM is not considered a medical act, and is therefore not reimbursed, which limits its use.

4. Pulse pressure (PP)

4.1. Definition of PP

About 80 to 90% of patients with cardiovascular events have at least one “classical” risk factor [53]. Diastolic BP was initially thought to be the best measure of risk, but the focus gradually shifted onto systolic BP and, more recently, PP. However, this variable, despite being well known to cardiologists is less frequently used by specialists in the field of diabetes.

Peripheral PP, most often measured at the site of the brachial artery, should not be confused with central PP, measured at the carotid site. Brachial PP is defined as the difference between the extremes of blood pressure (BP): systolic BP minus diastolic BP. Brachial PP as systolic BP overestimates central PP, especially in young subjects as, according to the “amplification phenomenon” (discussed later), the amplitude of the pressure wave is higher in peripheral arteries than in central arteries [54]. It is then inaccurate to use brachial PP as a surrogate for aortic or carotid PP, especially in young people [54]. Measurements of peripheral PP may be made in several ways: conventionally, with a sphygmomanometer, or by ambulatory blood pressure monitoring (ABPM). PP is a continuous variable and normal values vary across populations and have not been widely validated. However, when PP is treated as a qualitative parameter, a mean of 63 mmHg is generally taken as the upper limit of the normal range in untreated hypertensive subjects (52 mmHg for men and 49 mmHg for women), as high pre-treatment PP (defined using this threshold) is independently associated with subsequent CV disease and myocardial infarction, in particular [55]. If PP is divided into quartiles for the whole population, all-cause and total CV mortality are consistently higher in the group with PP ≥ 65 mmHg, for both normotensive men and hypertensive men and women [56].

Pathophysiologically, the existence of PP is a consequence of intermittent ventricular ejection from the heart. It depends on three haemodynamic factors: the pattern of left ventricular ejection, the capacities of large conduit arteries and the timing and intensity of wave reflections [57,58]. Proximal arteries, such as the aorta, play a major role in damping the pressure oscillations resulting from intermittent ventricular ejection. They ensure regular perfusion to peripheral tissues, even during the diastolic phase. Arterial stiffness (expressed as the
inverse of distensibility) affects the capacity of the arteries to dampen the pressure oscillations. After ventricular ejection, the BP waves propagate at a given speed (generally 5-7 m/second); although mean BP remains stable along the arterial tree, PP rises from the central to the peripheral arteries and this phenomenon is called PP amplification. The consequence of it is a significant increase of SBP together with a slight decrease of DBP. Two mechanisms are involved to explain these variations: firstly the pressure wave which goes from central to peripheral vessels which is restrained by the increasing rigidity of the arterial wall in association with a progressive reduction of vessel diameter; secondly, the fact that the BP curve is the summation of two waves: the first one which propagates from the heart to the peripheral vessels, and the reflected wave which returns toward the heart from specific vascular sites that could create resistance, such as bifurcations and calcified plaques [58, 59]. The final aortic BP wave is the sum of these two waves, the incident wave and the reflected wave. Arterial stiffness naturally increases from the aorta to peripheral small arteries.

Arterial stiffness and wave reflection are the two main determinants of increasing pulse pressure with age. Before age 50, brachial PP > aortic PP but due to rapid elevation of aortic stiffness with age and early return of reflection wave, PP becomes identical in all parts of the arterial tree in those > 50 years [58]. Several devices have been developed for evaluating and measuring large artery distensibility, compliance and wave reflections, but all require technical appraisal [54]. Carotid-femoral pulse wave velocity (PWV), is considered as the “gold standard” measurement of arterial stiffness [54]. It is a non-invasive method, and provides a direct, robust index of aortic stiffness. Briefly, aortic PWV is determined from waveforms obtained transcutaneously over the right femoral artery and the common carotid artery, the time lag between the feet of the two waveforms being recorded. The distance covered by the waves was estimated as the distance measured between the two recording sites. PWV = D (meters) / t (seconds) [60]. Brachial PWV determination requires the determination of pulse waveforms over the carotid and radial arteries. PWV is higher in stiffer arteries and correlations between brachial PP and PWV have been reported. Many methods for regional, local or systemic measurements of arterial stiffness are used and will not be developed here [54].

An increased arterial stiffness can increase the risk of coronary events as a premature return of the reflected wave in late systole increases central PP, thus systolic BP. Systolic BP increases the load on the left ventricle, increasing myocardial oxygen demand. For strokes, an increase of central PP could modify walls of arteries and the development of plaques [54].

4.2. Epidemiological data for different populations

Several epidemiological cross-sectional studies have shown that brachial PP is an independent marker of CV mortality, particularly in patients over the age of 50 years, in subjects with recurrent myocardial infarction, in older adults with congestive heart failure or stroke, and in normotensive and hypertensive men [56, 61–63]. Brachial PP provides useful information for predicting coronary heart disease [64, 65]. The risk of coronary heart disease in men with a PP ≥ 70 mmHg is more than three times that of men with a PP < 50 mmHg [66]. As both SBP and PP increase with resistance and stiffness, these two blood pressure components are highly correlated. However, when assessed individually, increases in brachial PP at a fixed systolic BP are associated with a greater risk of coronary heart disease than are parallel increases in systolic BP and diastolic BP at fixed PP [65]. PP recorded in the aortic root before angiography is significantly associated with the presence and extent of coronary artery disease [67]. The relative risk for CV mortality in male subjects with a brachial PP > 50 mmHg is 40% higher in normotensive patients and 48% higher in hypertensive patients than in patients with a PP < 50 mmHg [56]. Interestingly, the predictive value of ambulatory PP for CV risk is not significantly greater than that of office PP in essential hypertension [68].

Cross-sectional studies have shown that arterial stiffness, as assessed by determining PWV, is an independent marker of coronary artery disease [69]. It is now accepted that aortic stiffness is also an intermediate endpoint for CV events in patients with hypertension or end-stage renal failure [60, 70–72].

However, the situation is not quite so simple. Brachial PP which reflects both an increase in systolic BP and a decrease in diastolic BP with age, has provided only indirect evidence that arterial stiffness affects the likelihood of mortality. Moreover as already said, brachial PP may not accurately reflect aortic PP, because of the physiological amplification of PP between the central and peripheral arteries. The clinical situation is also less clear-cut than might initially appear to be the case. Firstly, the correlation between pulse pressure (brachial or central) and CV risk does not seem to apply to women [56, 67]. Secondly, the predictive value of PP for stroke remains unclear: reported to be significant in older adults whereas no significant association between brachial PP and cerebrovascular mortality has been found in another study [56, 63]. Thirdly, the positive association between brachial PP and CV risk sometimes disappears or is less strong after adjustment for systolic BP and affects its predictive value for CV events [73–75].

Concerns about antihypertensive treatments and PP variation in the general population will not be discussed here but nitrates increase arterial compliance in chronic hypertension by causing a selective decrease in systolic BP over diastolic BP which remains stable and a decrease of brachial PP, NO donors or enhancers of NO production and/or release might result in decreasing arterial stiffness [76]. Treatment with a combination of ACEi and diuretics seems to reduce systolic BP and central PP significantly more strongly than atenolol [77]. Diuretics and β-blockers have different effects on central PP, but no definite relationship between the effect of drugs on brachial PP and specific cardiovascular impact has been established [78]. It is also been suggested that BP-lowering drugs could have different effects on central aortic pulse pressure in a substudy of the ASCOT trial that could partially explain clinical differences in CV outcomes [1].
4.3. Data for patients with glucose intolerance or diabetes

Arterial stiffness results from several changes to the structure and function of large arteries: wall hypertrophy, calcium deposits, changes in the extracellular matrix, with an increase in the number of collagen fibres, fragmentation of the elastic deposits, changes in the extracellular matrix, with an increase in the number of collagen cross-links, have been reported [79]. Diabetes may itself modify wall structure, accelerating stiffening. Endothelial dysfunction and the formation of advanced glycation end products on the extracellular matrix, increasing the number of collagen cross-links, have been described. These phenomena, classically associated with ageing, seem accelerated by diabetes [80].

4.3.1. Aortic stiffness

In the cross-sectional ARIC study, aortic stiffness was found to increase in patients with glucose intolerance or type 2 diabetes [81]. In another study of subjects with glucose intolerance or type 2 diabetes followed up for 10 years, aortic stiffness was found to be a powerful independent predictor of mortality in patients with hyperglycaemia and a better prognostic factor for mortality than systolic BP. Aortic PWV is higher in subjects with hyperglycaemia than in those with normoglycaemia, for all values of systolic BP. The mortality rate of patients with glucose intolerance is higher than that for patients with normoglycaemia, with a relative risk of 2.12 (1.11-4.00). Classical risk factors, such as age, sex ratio and systolic BP, are predictive of mortality, but PWV independently predicts all-cause and CV mortality, with a relative risk of 1.08 for each 1 m/s increase [82].

4.3.2. Pulse pressure

In a prospective study, brachial PP was measured in 140 patients with recent glucose intolerance. After a median follow-up period of seven years, PP was found to be positively associated with all-cause mortality, with a relative risk of 1.7 (1.2-2.5), even after adjustment for confounding factors, including the presence of hypertension [83]. The Hoorn Study (a Dutch population-based cohort study of 2484 patients, including 208 patients with type 2 diabetes aged 50-74 years) reported the incidence of cardiovascular deaths after a median follow-up period of nine years. The patients who died had a higher brachial PP than the patients who survived: 60 ± 17 versus 52 ± 15 mmHg (P = 0.003). In diabetic patients, the risk of cardiovascular death increased by 27% for every 10 mmHg increase in PP. The association between PP and all-cause mortality is weaker (RR: 1.12; 0.93-1.34). The stronger association between mortality and PP at a given age for diabetic than for non-diabetic subjects suggests that type 2 diabetes accelerates vascular ageing [84]. The authors reported that the associations of cardiovascular and all-cause mortality with PP were somewhat but not significantly stronger than those with systolic BP, but did not present their data. The editorialist estimated however that PP cannot replace systolic BP as a single measure of CV risk, because systolic BP rises with increases in both resistance and arterial stiffness [85]. In a cohort of elderly patients with type 2 diabetes and previous CV events, a U-shaped association between PP and mortality was observed, possibly due to arterial stiffness and heart failure [86]. Another study in 2911 patients with type 2 diabetes showed that, during a four-year follow-up period, PP was a better predictor of coronary heart disease risk than either systolic BP or diastolic BP. Neither systolic BP nor diastolic BP contributed any additional value for defining coronary heart disease risk beyond that provided by PP alone. Conversely, both systolic BP and diastolic BP predicted the risk of cerebrovascular and peripheral vascular events after correction for confounding factors, but systolic BP performed slightly better [87]. The editorialist agreed that PP is strongly predictive of CV events but suggests that the differences in the predictive value of PP and systolic BP for vascular beds should be interpreted with caution for statistical reasons [88]. Finally, even when normotension is achieved, an increased brachial PP remains a significant independent predictor of mortality in diabetic patients [89].

The prognostic value of ambulatory 24-hour PP for vascular events was studied in 228 relatively young subjects (mean age: 46 years) free of complications. When the subjects were stratified into quartiles, in the widest quartile (cut-off point 53.3 mmHg), the incidence of CV events was 21% over a 100-month follow-up period (vs 4% in the narrowest quartile; P < 0.001) whereas no difference was observed for cerebrovascular events [90].

The first study to report an association between increases in PP and diabetic complications was published in 2002. Among 80 patients with type 2 diabetes, nocturnal brachial, but not diurnal PP was higher in patients with retinopathy than in those without retinopathy. In patients with macroalbuminuria, both diurnal and nocturnal PP were higher than those in patients with normoalbuminuria (nocturnal PP: 70 ± 15 mmHg in patients with macroalbuminuria vs 54 ± 9 mmHg in patients with normoalbuminuria; P < 0.001). The difference in PP between patients with micro- and normoalbuminuria was not significant. Patients with macrovascular disease had significantly higher nocturnal PP than patients without this condition, due to larger increases in systolic BP than in diastolic BP. The authors suggest that increases in brachial PP could greatly increase shear stress in the microvasculature, resulting in capillary/glomerular hypertension and the development of micro- and macrovascular complications. One limitation of the study was the lack of comparison of the predictive value of PP with that of systolic BP and the lack of consideration of other confounding risk factors in the prediction of complications. These haemodynamic abnormalities may result from or contribute to the development of diabetic complications, and further prospective studies are required to clarify the situation [91]. Conflicting data have been obtained concerning microalbuminuria and PP, as in patients with type 2 diabetes and incipient nephropathy (microalbuminuria ≥ 3 mg/mmol and creatininaemia < 153 μmol/L) systolic BP, PP and PWV are higher than in patients with normoalbuminuria (P < 0.05) [92]. Even modest renal dysfunction may increase arterial stiffness, an independent risk factor for CV disease, and differences in the conclusions may result from differences between the populations studied [91,92]. In elderly diabetic
patients, ambulatory 24-hour PP is independently and significantly associated with the progression of albuminuria and may provide additional information for predicting this progression, whereas this is not the case for office PP [93]. PP has also been shown to be associated with CV risk in diabetic patients with renal failure [94]. In a cross-sectional study on French Afro-Caribbean patients with type 2 diabetes undergoing haemodialysis (30% with cardiovascular disease), predialysis PP was found to be strongly associated with CV events. However, it was not possible to determine whether the increase in PP preceded the occurrence of CV events, due to the design of the study [95].

Few studies have focused on patients with type 1 diabetes. One such study demonstrated higher levels of carotid stiffness in patients with uncomplicated diabetes than in patients without diabetes [96]. In a large cohort of diabetic patients from the EURODIAB study (median age 33 years), PP was found to be related to ageing and was a prognostic factor for CV complications over a seven-year follow-up period. In the general population, diastolic BP is generally predictive of CV outcome in younger subjects, whereas systolic BP and PP are predictive of CV events in older subjects. Thus, in young patients with type 1 diabetes, PP is a major determinant of CV complications. It may reflect a more advanced arterial age and stiffness in these patients than would be expected from their chronological age. The increase in PP with age is more pronounced in patients with initial micro- or macroalbuminuria and retinopathy, suggesting that the progression of arterial ageing is more pronounced in the presence of target organ damage [97].

5. Limitations to consider PP as a surrogate marker of CV risk in clinical practice

There could be a confusion between brachial PP, easy to study in epidemiological studies, and central PP which more precisely reflects central arterial stiffness but which needs more sophisticated techniques and is applicable in research or in clinical trials. After that, there are certain caveats to consider brachial PP as a surrogate marker of CV risk [reported in 85]. Firstly, PP can be affected by changes in heart rate or cardiac contractility. Secondly, PP is influenced by the phenomenon of peripheral amplification: the usual progressive amplification of the PP from the aorta to the brachial artery decreases with ageing as central elastic arteries stiffen and explains the gradual shift from diastolic BP to systolic BP and to PP as predictors of CV risk in older patients. On the contrary, in middle-aged healthy people or in older patients with systolic and diastolic hypertension or in patients with diabetes, systolic BP is equal or superior to PP as predictor of CV risk. Then, both systolic BP and PP must be jointly placed in a Cox regression model to assess CV risk in patients with diabetes. [85]. Moreover, it was recently reported that the strength of the correlation between aortic and carotid stiffness weakens as the number of cardiovascular risk factors increases, particularly in cases of high BP or diabetes [98]. Moreover, it remains difficult to analyze the impact of antihypertensive treatments on PP, particularly with respect to their impact on confounding factors, such as age. A small study, in which perindopril was administered randomly to patients with type 2 diabetes suggested that carotid distensibility increases in a dose-dependent manner, and independently of mean PP which remain unaffected by dose titration, as measured by ABPM [99]. Finally, the very interesting observation that drugs able to reduce central PP despite similar reduction of systolic BP may have more beneficial effects on the prognosis of CV remains unproven for diabetic patients [1].

6. Conclusion

The two markers night/day variations and PP are very different and no hierarchy is possible between them to predict CV risk. However, study of circadian blood pressure profile could be informative in the diabetic population: patients with a blunted decrease in nocturnal BP have a high risk of developing micro and macrovascular complications, particularly in case of hypertension, but also in normotensive patients with diabetes. The small or non-existent nocturnal decrease in BP reflects the high CV risk of these patients. The alteration of circadian blood pressure profile has direct clinical applications: ABPM recordings suggestive of a reverse circadian BP profile should alert the physician to the potential risk of complications and provide justification for the effective treatment of hypertension, especially at night. They should also lead the physician to check for a sleep apnoea syndrome, particularly in cases of resistant hypertension, or autonomic neuropathy (postural hypotension), a well known risk factor for CV events. Patients should be carefully screened for nephropathy. Few treatments have yet been defined, with only non-specific treatments such as ACEi, diuretics, salt restriction, and the maintenance of available CPAP. However, the potential benefits on nocturnal BP and CV events of taking blood pressure-lowering drugs at bed time rather than in the morning in non dippers remain to be confirmed in terms of CV morbidity and mortality.

Concerning the other component, the conclusion is that brachial PP is an independent predictor of cardiovascular mortality in the diabetic population, but not of all-cause mortality. It is associated with diabetic complications for both type 2 and type 1 diabetes. This association is stronger for nocturnal than for diurnal PP and PP is strongly predictive of coronary heart disease in patients with type 2 diabetes. The stronger association between PP and age in the diabetic than in the non-diabetic population suggests that type 2 diabetes leads to the acceleration of vascular ageing. In type 1 diabetes, PP is associated with macrovascular complications, possibly providing further evidence of accelerated vascular ageing, whereas the predictive value of this factor is rather encountered in older patients in the general population. Brachial PP increases CV risk in patients with incipient nephropathy or overt renal failure. However, peripheral stiffness seems to be less strongly correlated to aortic stiffness, as CV risk increases in diabetic patients. Data about central PP are missing in diabetic populations, particularly concerning impacts of treatments.

Finally, these two components explore different aspects of variations of blood pressure, and in the general population as in diabetic patients, it is not possible to compare them for estima-
tion of cardiovascular risk. Measurements of circadian variations of blood pressure or brachial PP seem easy in clinical practice but estimation of central PP requires a higher degree of technical expertise. However, in recent recommendations, central PP measurements should be considered as recommended tests for the evaluation of cardiovascular risk, particularly in patients in whom target organ damage is not discovered by routine investigations [53]. Studies are needed in diabetic patients.

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