Blood Pressure, Heart Rate Variability, and Renal Function in Nonsmoker and Smoker Hypertensive Patients

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In this issue of the Journal, Liakos and coworkers[1] report the results of a cross-sectional study aimed at investigating the correlation of 24-hour blood pressure (BP) and heart rate (HR) variability, as assessed by a single session of 24-hour ambulatory BP monitoring, with renal function in a large cohort of untreated, uncomplicated essential hypertensive patients. In particular, the authors examined the influence of smoking status on the relationship between BP/HR variability and renal parameters including creatinine clearance, estimated glomerular filtration rate, albumin-to-creatinine ratio and urinary α_1-microglobulin. Before addressing the details of the study, available evidence on this issue and related topics should be considered.

Strong evidence supports the view that cardiac and extracardiac markers of hypertensive organ damage are more closely related to home and ambulatory BP than to office BP. Furthermore, numerous studies have shown that organ damage also correlates with standard deviation of 24-hour BP, suggesting that the adverse consequences of hypertension on cardiovascular function and structure reflect both average 24-hour BP elevations and BP variability. In a pioneering study published in the early 1990s, Frattola and coworkers[2] provided the first longitudinal evidence of the impact of BP variability on target organ damage. Seventy-three patients with essential hypertension who had their 24-hour ambulatory BP monitored intra-arterially by the Oxford technique were re-examined after 7 years or more. According to multiple regression analysis, a significant correlation was found between overall organ damage score at follow-up evaluation (electrocardiographic and/or echocardiographic left ventricular hypertrophy, retinopathy, and renal dysfunction) and initial level of organ damage, long-term BP variability (among half-hour standard deviation of 24-hour mean BP) at the initial evaluation, and clinic BP at follow-up. This was not the case for short-term BP variability (within half-hour BP standard deviation), presumably because this index represents a minor component of overall BP variability.

After this seminal paper, increasing evidence has accumulated on the association of BP variability with a variety of manifestations of subclinical organ damage. Several studies have shown that BP variability as assessed by different parameters (ie, 24-hour BP variability, visit-to-visit variability) is related to increased endothelial damage and arterial stiffness.[3,4] Other studies have reported that inflammatory markers of vascular damage, such as C-reactive protein, soluble E-selectin, tumor necrosis factor α, and interleukin 6 levels, are increased in patients with elevated 24-hour BP variability.[5] Finally, investigations performed in different clinical settings have provided evidence that increased BP variability, in addition to increased average BP levels, is an independent predictor of development and progression of renal disease as well as of cardiovascular events and mortality.[6] In a post hoc analysis of the Reduction of End Points in Non-Insulin-Dependent Diabetes With the Angiotensin II Antagonist Losartan Study and the Irbesartan Diabetic Nephropathy Trial, including a total 2739 participants with type 2 diabetes and nephropathy, McMullan and coworkers[7] analyzed the association of visit-to-visit systolic BP variability with renal and cardiovascular morbidity and mortality among individuals with diabetes and nephropathy. A greater visit-to-visit variability of systolic BP (calculated from the standard deviation of systolic BP during 4 visits within 3 to 12 months post-randomization) was independently associated with increased risk of the composite renal disease endpoint and end-stage renal disease, but not with the cardiovascular outcome. In a cohort of 1618 patients with stage 2 to 5 chronic kidney disease, visit-to-visit systolic BP variability was significantly and independently related to baseline office BPs, age, glucose, and estimated glomerular filtration rate (eGFR). Both standard deviation of systolic BP and variation coefficient of systolic BP were significant predictors of the combined endpoint (death and incident cardiovascular events) after adjusting for confounders.[8]

Seventy years ago, Levy and coworkers for the first time documented an association between a faster HR and cardiovascular disease.[9] In the past 4 decades, several authors have consistently shown that a higher HR is a strong risk factor for cardiovascular morbidity and mortality as well as for noncardiovascular death. More recently, the clinical and prognostic value of HR variability has been extensively investigated in patients with coronary artery disease, congestive heart failure, asymptomatic left ventricular dysfunction, valve disease, and essential hypertension. The majority of studies have demonstrated that individuals with reduced or abnormal HR variability have an increased likelihood of

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subclinical cardiac damage as well as a higher risk of cardiovascular mortality. Various measures of HR dynamics, such as time-domain, spectral, and nonlinear measures of HR variability have been used for stratifying cardiovascular risk. In the mid-1990s, Mandawat and coworkers[10] showed that patients with left ventricular hypertrophy secondary to hypertension or aortic valve disease had a higher left ventricular mass index and reduced HR variability compared with controls. Furthermore, in that study, an inverse relationship was found between HR variability and left ventricular mass index ($r=-0.478$, $P<.001$). In one study evaluating right ventricular remodeling, HR variability, and their interaction in untreated hypertensive patients, we found that alterations in right ventricular structure, function, and dynamics were associated with impaired HR variability.[11]

Decreased HR variability associated with increased risk of end-organ damage and cardiovascular events has also been reported in the setting of chronic renal disease over a wide range of ages in nondiabetic and type 1 and 2 diabetic populations.[12]

It has long been recognized that, in addition to day-night BP changes, 24-hour BP and HR are characterized by short-term variations that are more evident and frequent during daytime but also present, although less pronounced, during the nighttime period.

These variations are largely dependent on behavioral activities, such as physical activity, job stress, and smoking. Strong evidence supports the view that smoking causes an imbalance of the autonomic nervous system; in particular, tobacco smoke increases sympathetic activity resulting in BP and HR elevation.[13]

The report by Liakos and coworkers[1] provides a new piece of evidence on the association between BP, HR, and renal function in a large sample of adult untreated essential hypertensive patients without diabetes and renal insufficiency, stratified according to cigarette smoking status. The prevalence of active smokers at the time of examination was approximately 38%, and about two thirds were men. BP and HR variability were calculated as coefficients of variations derived from 24-hour ambulatory recording. In the total population, systolic 24-hour BP variability was inversely related with creatinine clearance (CrCl) and eGFR; this correlation failed to achieve statistical significance after adjusting for age, sex, and smoking status. Similar findings were obtained in the fraction of smoker hypertensives. Systolic 24-hour BP variability showed a positive relationship with albumin/creatinine ratio and α_1-microglobulin in the whole sample as well as in the three smoking subgroups. It should be noted, however, that average 24-hour systolic BP was more strongly correlated with all above-mentioned renal parameters than 24-hour BP variability. This important finding conveys the concept that the magnitude of BP variations during daily life has a lower impact on renal damage than the absolute BP load in essential hypertensive patients without comorbidities. A further relevant result provided by Liakos and coworkers is the notion that 24-hour HR variability was positively correlated with renal function, a difference from 24-hour BP variability. HR variability, indeed, was positively related to CrCl and eGFR, and inversely related to albumin/creatinine ratio and α_1-microglobulin; the strength of this relationship was statistically significant in the total sample as well as in all subgroups. This suggests that reduced HR variability may be associated with subtle alterations in renal function even in patients without evidence of overt kidney disease. Interestingly, this trend was more evident in current smokers than in nonsmokers and former smokers. This observation is in line with clinical studies showing a powerful correlation between cigarette smoking and worsening renal function in patients with hypertension, diabetes, and chronic renal disease.[14] Renal effects of nicotine include transitory increases in BP paralleled by reductions in renal perfusion, increased generation of reactive oxygen species, and activation of profibrotic pathways. A few additional points deserve to be discussed. First, average 24-hour HR, at variance from 24-hour variability, was found to be unrelated to renal parameters in the total cohort as well as in smokers. This negative finding is in keeping with previous literature data. A lack of an independent association between HR, derived from 48-hour ambulatory BP monitoring, and markers of cardiac and extracardiac target organ damage, such as left ventricular hypertrophy, carotid atherosclerosis, and microalbuminuria, was shown by our group in 580 never-treated hypertensive patients.[15] Average 48-hour HR, indeed, was similar in patients without organ involvement and in those with one, two, or three markers of organ damage. Second, the study by Liakos and coworkers confirms and extends to a large cohort of uncomplicated hypertensives the notion that cigarette smoking acts as a powerful risk factor for renal damage by showing that a significant relationship exists between the pack-years amount and subclinical renal impairment.[16] Third, the strengths of the present study are the large, carefully selected population and the exclusion of patients taking antihypertensive medications, as drug treatment is known to affect the relationship between BP/HR and organ damage. Finally, as recognized by the authors, major limitations are represented by the cross-sectional nature of the design and the estimate of HR variability based only on data provided by ambulatory BP monitoring rather than by 24-hour electrocardiographic recording. Despite these limitations, the study clearly supports the view that the impact of hypertension on renal function may depend on HR variability, particularly in smokers.

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