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Perirenal Fat and Disrupted Circadian Blood Pressure Patterns

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Ambulatory blood pressure monitoring (ABPM) provides a comprehensive assessment of BP over a 24-h period capturing abnormal BP phenotypes not detectable in the clinical environment such as white coat, masked hypertension, and non-dipping (ND) or reverse dipping pattern [1, 2]. ABPM has a unique ability to record BP changes throughout the day allowing us to estimate the extent of the physiological BP fall at night [3]. This information has great clinical and prognostic relevance as a large amount of evidence have emerged about the excess cardiovascular (CV) risk linked to a blunted nocturnal BP fall both in the general population and in the adult hypertensive setting. For over four decades the phenotyping of circadian BP changes has been relying on the classification in dippers (D) (i.e., night-time BP $\geq$ 10% lower than day-time values and ND (i.e., night-time BP fall $<$ 10%) [4].

The loss of physiological BP nocturnal drop is due to multiple pathophysiological mechanisms and factors acting individually or, more often, in association with each other. In the hypertensive setting, these include ethnicity; age; gender; comorbidities such as obesity, obstructive sleep apnea (OSA), diabetes, and chronic renal disease; daytime physical activity; quality and duration of sleep; indoor ambient temperature; seasonality; and antihypertensive treatment schedule.

Obesity may impair health outcomes through numerous pathways, including insulin resistance, dyslipdemia, and increased secretion of pro-inflammatory cytokines by enlarged fat cells and over-activation of the sympathetic nervous system. In particular, adrenergic overdrive associated with obesity and enhanced by the presence of comorbidities has been shown to play a pivotal role in altering the BP circadian rhythm [5].

In the context of research aimed at clarifying the regulatory mechanisms of circadian variations in BP and, in particular the role of visceral fat, the study by Wu et al. [6] published in this journal provides new insights into this intriguing issue targeting the link of perirenal fat thickness (PRFT), a new metric of adiposity, with an altered circadian BP profile and short-term BP variability in patients with essential hypertension, compared to conventional adiposity indices. For this purpose, cross-sectional data of 253 hospitalized hypertensive patients (mean age 45 years, 34 % women, body mass index [BMI] 26.3 kg/m^2, 11.5% with OSA and 8.7% with type 2 diabetes) were analyzed revealing that the prevalence of the extreme abnormal nocturnal BP phenotype (i.e., reverse dipping pattern) increased progressively from the first to the third tertile of PRFT, determined by computed tomography (CT). This was also the case for morning and nocturnal hypertension but not for short-term BP variability.

Before commenting in more detail on the new contribution of this study, we believe that it may be appropriate to focus on two important aspects that allow for a better understanding of the state of the art in this research area: (I) the current evidence on the association of BMI, a time-honored index commonly used in clinical practice to define overweight and obese categories and abnormal 24-h BP profile; and (II) the clinical and prognostic significance of PRFT.

The relationship between obesity, phenotyped via BMI metric, and altered nocturnal BP patterns has been recently studied across different age groups and clinical settings. A retrospective study carried out in 263 children/adolescents with elevated BP (70 normal weight, 33 overweight, 55 class I obesity, 53 class II, and 52 class III obesity) documented that the prevalence of systolic ND increased progressively with severity of obesity (i.e., class I = 38%, class II = 45%, class III = 52%, $p = 0.008$) [7]. In a large cohort of 499 Chinese adolescents with overweight and obesity, Zhou et al. [8] demonstrated that increasing severity of obesity was associated with a higher risk of ND status only in girls but none in boys, thus suggesting that this association was sex dependent. As expected, the available evidence in the adult setting is more abundant than that in the pediatric population. In an early study by our group [9], 658 consecutive never treated patients with grade 1 and 2 hypertension, undergone ABPM over two 24-h periods within 4 weeks, were classified as lean or overweight/obese and, according to the consistency of the dipping or ND status in the first and second ABPM periods, as reproducible dipper, reproducible ND, and variable dipper. The prevalence of reproducible ND was significantly higher in overweight/obese than in their lean counterparts (men = 27% vs 20%, women = 28% vs 22%, $p < 0.05$).

Mechanisms Underlying Stress and Emotions (MUSE) in African American Women's Health Study examined circadian BP changes across BMI categories in a cohort of early middle-aged women. Unlike overweight participants and those in obesity classes I and II, the systolic BP of women with obesity class III declined more slowly from day to night, resulting in a markedly higher prevalence of ND [10]. In a mixed population of 6967 normotensive and hypertensive patients, the risk of being ND was 42% higher in obese individuals than in normal weight individuals [11]. Furthermore, subgroup analysis revealed that this association persisted both in treatment naïve and treated hypertensives adults but not in normotensives. Awareness of the limitations of BMI as a reliable indicator of adiposity has led in recent decades to testing the clinical and prognostic significance of different obesity metrics such as waist circumference (WC), visceral body tissue, subcutaneous adipose tissue, epicardial adipose tissue, and PRFT. These lines of research have suggested that the regional fat distribution is more important than BMI (which actually does not provide accurate information about fat and lean components) in capturing obesity-related outcomes [12].

Contrary to what was previously believed, PRFT is not an inert tissue with an energy reservoir function and mechanical protection of the kidney but like other visceral adipose depots is a biologically active visceral fat tissue that releases adipocytokines, proinflammatory mediators, and other bioactive molecules, which play a role in determining the development of various CV and systemic diseases [13]. Furthermore, it has been suggested that, independently from the mediators mentioned above, the accumulation of fat at the level of the renal hila can result, through a compressive mechanism, in an increase in hydrostatic pressure and in the activation of the renin–angiotensin–aldosterone system promoting a cascade of unhealthy conditions such as hypertension, insulin resistance, and subclinical vascular damage [14]. A meta-analysis of 10 studies comprising a pooled population of 1221 children and 4767 adults showed that PRFT, assessed by CT or ultrasonography, was significantly associated with common carotid intima media thickness (CIMT) [15]. Further evidence of a relationship between PRFT measured by CT and subclinical target organ damage was recently provided by a study conducted on 1112 individuals with type 2 diabetes mellitus divided into two groups with (25.7%) and without (74.3%) echocardiographic left ventricular hypertrophy (LVH) [16]. Patients belonging to the LVH group exhibited significantly higher PRFT (16.5 ± 3.8 mm) than those with normal LV mass index (LVMI) (11.7 ± 4.3 mm, <0.001). After adjustment for confounding factors, both LVMI ($b = 0.262$, $p < 0.001$) and LVH (OR: 1.33, 95% CI: 1.24–1.43, $p < 0.001$) persisted to be positively associated with PRFT.

A significant correlation between ultrasonographically determined PRFT and office systolic BP was reported by Ricci et al. [17] in a cohort of 284 morbidly obese patients regardless of whether they were normotensive or hypertensive. Interestingly, in the subgroup of hypertensive patients who underwent sleeve gastrectomy, a positive correlation was found between pre-intervention PRFT and post-intervention decrease in systolic BP, as well as in the number of BP lowering drugs. A prior study by De Pergola et al. [18] addressing the relationship between ultrasonographic PRFT and 24-h ABPM in 42 normotensive overweight/obese individuals revealed that this index of visceral adiposity was uniquely correlated with 24-h diastolic BP, but not with daytime or nighttime systolic/diastolic BP.

The study by Wu et al. [6] adds a new piece of information on the potential relationship between PRFT and out-of-office BP in the hypertensive setting, focusing, in particular, on its link with altered BP phenotypes such as reverse dipping pattern, morning hypertension, and nocturnal hypertension. Unlike previous studies conducted in morbid obese patients with heterogeneous BP status [17] or normotensive overweight/obese individuals [18] the authors found that increasing PRFT tertiles were associated with a graded, significant increase in mean 24-h, daytime and nighttime ambulatory systolic/diastolic BP values [6]. This BP trend was paralleled by an increase in prevalence rates of reverse dipping pattern across PRFT tertiles (I = 7%, II = 13%, III = 20%, $p = 0.04$), morning hypertension (I = 40%, II = 59%, III = 69%, $p < 0.001$) and nocturnal hypertension (I = 63%, II = 79%, III = 88%, $p < 0.001$). Adjustment for multiple confounders confirmed the persistence of the association of PRFT with morning or nocturnal hypertension but not with a reverse dipping pattern. It may be related to the fact that only 34 of the patients (13%) included in the study presented this relatively infrequent abnormal BP phenotype, and this may have impacted on its actual association with PRFT. However, it should be noted that no significant relationship was found even when extending the correlation analysis to ND and reverse dipping treated as a single group ($N = 148$, 58.5%) raising doubts about the ability of PRFT to capture circadian BP alterations. Although the study by Wu et al. [6] demonstrates that PRFT outperforms BMI (and other conventional paraters of adiposity) in identifying disrupted circadian BP patterns, the results cannot be extended to populations with different clinical characteristics and ethnicity. In fact, the patients studied were of Asian ethnicity and had a very high prevalence of nocturnal hypertension (76%).

Finally, the translational perspectives of this study, based on a not easily accessible diagnostic tool such as abdominal CT, remain elusive. An alternative way could be the inclusion of the PRFT assessment in the course of routine renal ultrasound examination as a complementary diagnostic parameter, if future studies will support an additional value of this index in refining clinical and therapeutic decision-making in the hypertensive setting [19, 20].

Author Contributions

C.C., M.T., and G.G. contributed equally to the literature review, manuscript setup, and final revision of the manuscript. C.C. prepared the first draft.

Conflicts of Interest

The authors declare no conflicts of interest.

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