

**WHITE COAT HYPERTENSION: WHEN OFFICE BLOOD PRESSURE IMPACTS CARDIAC
MECHANICS MORE THAN AMBULATORY.**

IS THIS REALLY SO?

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Hypertensive heart disease, characterized by left ventricular hypertrophy (LVH), left atrial enlargement and LV dysfunction, represents a relatively advanced stage of hypertension-mediated organ damage (HMOD) typically associated with unrecognized or inadequately controlled systemic hypertension. However, a growing amount of evidence supports the view that subtle cardiac morpho-functional abnormalities such as LV concentric remodeling and mild impairment in LV relaxation can develop very early in the natural history of hypertension. Furthermore, an increased risk of initial cardiac HMOD has also been reported for long-held innocent conditions such as pre-hypertension and white coat hypertension (WCH).

WCH is a common condition in which blood pressure (BP) measured in the medical environment is elevated while out-of-office BP (i.e. home and/or ambulatory BP) is normal (1). The relationship between WCH and cardiac HMOD, an intermediate step linking hypertension with overt cardiovascular disease, has been investigated by numerous individual studies and their meta-analyses. Pooled data from 25 studies, including a total of 7.382 untreated individuals (2.493 true normotensives, 1.705 WCH and 3.184 sustained hypertensives), showed that LV mass index (LVMI) gradually increased from normotensive, WCH, to sustained hypertensive patients. A meta-regression analysis restricted to WCH group documented a significant direct correlation between LVMI and office systolic BP ($r=0.42$, $p<0.01$); this was not the case for day-time systolic BP ($r=0.18$, $p=0.17$). Of note, the meta-analysis suggested that LV relaxation (in parallel with a greater left atrial size) but not LV ejection fraction (LVEF) was impaired in WCH (2).

Thus, whether WCH can affect LV systolic function remains entirely undefined as current evidence on this important issue is based almost exclusively on the assessment of LVEF, a well established and reliable index but not sensitive enough to detect subtle changes in systolic function.

Recent evidence supports the view that LV mechanics and, in particular, global longitudinal strain (GLS), have better diagnostic sensitivity and reproducibility than LVEF irrespective of vendor and level of echocardiographic training and, more importantly, better prognostic value

than LVEF in large spectrum of cardiovascular conditions (including hypertension) and general population.

Starting from this premise, we sought to investigate, using 2D and 3D speckle tracking (STE) echocardiography, whether LV mechanics were impaired in WCH patients with normal LVEF. Thus, for the first time, we were able to show that both GLS and global circumferential strain were significantly lower (worse) in WCH than in normotensive controls (-19.4 ± 2.6 vs $20.9 \pm 3.0\%$, $p < 0.05$, and -20.1 ± 2.7 vs $21.6 \pm 2.8\%$, $p < 0.05$, respectively) (3). Whereas no difference in LVEF was found between the two groups. It should be pointed out that WCH and normotensives had completely overlapping demographic/clinical characteristics (age, sex, body mass index, metabolic variables and prevalence of current smoking) and, more importantly, average 24-hour, day-time and night-time BP values (i.e. systolic BP 116 ± 6 vs 115 ± 6 mmHg, 119 ± 7 vs 118 ± 7 mmHg, 108 ± 6 vs 106 ± 6 mmHg, respectively). This finding seems to suggest the hypothesis that transient BP rises, such as those triggered by stress-related sympathetic activation during clinical visit, are enough to adversely affect LV systolic function, regardless of the ambulatory BP (ABP) values. Although this view may be plausible as the white coat effect is commonly believed to be associated with marked sympathetic and hormonal activation, it deserves, however, to be taken with extreme caution, considering the following issues.

First, the definition of WCH based on a single ABPM is largely inaccurate because ABP values may vary from one session to another due to changes in environmental stimuli, physical activity and sleep quality. A limited short- and long-term reproducibility of the WCH pattern has been reported by numerous studies. Our group documented that approximately 50% of the patients diagnosed as having WCH by the first ABPM, daytime BP values obtained at a second ABPM within 1–4 weeks were >135 mmHg systolic or 85 mmHg diastolic, shifting them into the category of sustained hypertensives. Second, large studies conducted both in hypertensive cohorts and in samples of the general population have shown that WCH individuals still have

mean values of out-office BP (home or ambulatory) higher than normotensive ones. In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study, carried out in an Italian population sample, participants with WCH had mean 24-hour systolic and diastolic BP values of 5 mmHg and 3 mmHg higher than their true normotensive counterparts (4). Third, it has been demonstrated that an isolated elevation of night-time BP may be present in about 30% of individuals with WCH when this phenotype was primarily defined on the basis the 24-hour or day-time BP normality. Finally, to the best of our knowledge, no other study on cardiac mechanics in WCH has been published so far.

Furthermore, the hypothesis that out-office BP in WCH patients has a marginal role on subclinical HMOD and, particularly on cardiac mechanics is further challenged by reports suggesting that ABP is more closely associated with changes in LV longitudinal deformation than that office BP. Sera et al. addressed the association of BP control with GLS using ABP and office BP criteria in a community-based, elderly cohort of 394 hypertensive individuals with normal LVEF (5). After adjustment for several confounders, uncontrolled 24-hour ABP remained significantly associated with abnormal GLS, whereas uncontrolled office BP was not. A significant association with abnormal GLS was also found using either daytime or night-time criteria. In a subsequent study by the same research group carried out on 577 participants from the Cardiovascular Abnormalities and Brain Lesions (CABL) study all ABP measures (24-hour, day-time and night-time) were more closely associated with impaired GLS than office BP ones. In line with these data, some studies have shown that alterations in LV mechanics are present in individuals with masked hypertension (i.e. the opposite condition to WCH), characterized by normal BP values measured in the office not confirmed by ABPM.

Therefore, future studies are needed to clarify whether early alterations in LV longitudinal function described in patients with WCH is truly independent of out-office BP. To this purpose,

however, a more precise phenotyping of the WCH pattern (based on the agreement of two ABPM and using as diagnostic criteria the mean values of 24 hours, day-time and night-time) is mandatory.

So further evidence supporting the view that early changes in LV systolic function not detectable by conventional echocardiography in the WCH setting can be unmasked by STE could significantly improve cardiovascular risk stratification and consequently help guide therapeutic decisions in these patients for whom drug treatment is only recommended when the cardiovascular risk is high or very high.

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