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Commentary

Tachycardia as a cardiovascular risk factor. Role of ambulatory heart rate

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There is a large body of evidence that resting Heart Rate (HR) is a strong predictor of cardiovascular events and mortality in hypertension [1,2]. This association was consistent across 9 Cohort studies and 7 large clinical trials performed on patients with hypertension [1]. However, in a pioneer study performed with intra-arterial recording Prof Mancia and Coworkers in Milan showed that the medical visit elicits an important hemodynamic reaction with a rise in blood pressure, leading office measurements to overestimate the usual blood pressure of the patients [3]. In the same study, the authors showed that a marked rise during the medical visit occurred also for resting HR, which lasted for a long period after the visit. This could suggest that, as is the case with blood pressure, HR measured over 24 hours may provide better prognostic information than conventional HR measurement obtained in the clinical setting.

This hypothesis was explored in the ABP-International study by Palatini, et al. [4]. This is a multicentre study involving over 7 thousand hypertensive patients recruited in 8 Centers around the world, in whom ambulatory HR was measured.

In that study we showed that the association of ambulatory HR with cardiovascular events was stronger than that of office HR, confirming the results of previous smaller studies [4]. In a multivariable model, among the ambulatory sub-periods, night-time HR emerged as the strongest predictor of outcome with a 13% increase in risk for a 10 bpm increment in HR.

Similar results were later found in the Spanish Registry which collected the largest ever number of hypertensive patients assessed with 24-hour recordings [5]. In that study, participants were stratified into 4 daytime and nighttime groups with HR intervals spanning from below 60 to over 90 bpm. For all outcomes night-time HR was a stronger predictor than daytime HR, in particular for total mortality, cardiovascular mortality, and even noncardiovascular mortality.

In a Belgian study in middle-aged men followed for 16 years, it was shown that ambulatory HR predicted mortality on top of office HR. Office HR was an independent predictor of mortality, but after multivariable adjustment including ambulatory HR, the association was no longer significant [6]. In contrast, ambulatory HR remained an independent predictor of outcome also after multivariable adjustment and after office HR was included in the model.

The superiority of ambulatory over office HR was further proved by a more recent analysis of the ABP-International dataset [7]. Alike with BP, we divided the subjects according to whether they had a normal office and nigh-time HR, white-coat tachycardia, that is high office and normal ambulatory HR, masked tachycardia, and sustained tachycardia. The results showed that no increase in the risk of cardiovascular events was present for white-coat tachycardia, whereas people with masked tachycardia and sustained tachycardia had a noticeable increase in risk. Again, this proves the superiority of ambulatory HR over office HR for the prediction of adverse outcomes.

The association of both office and ambulatory HR with cardiovascular events and mortality has been found either in general populations or in hypertensive cohorts at any age ranging from adolescence to old age [1,2]. In addition, HR has shown an important predictive capacity also in patients with cardiovascular diseases including myocardial infarction, congestive heart failure, and stroke [1,2].

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Ambulatory HR, and night-time HR, in particular, have also been found to be associated with organ damage in hypertension. In a study by Prof Redon group in Valencia, among the ambulatory HRs only nocturnal HR was associated with composite cardiac, carotid, and renal damage [8]. Within the frame of the HARVEST study in Italy, we obtained similar results for large artery stiffness [9]. In the participants grouped by asleep HR at baseline, nighttime HR was an independent predictor of central blood pressure, and the augmentation index measured 8 years later. In an elderly cohort of 680 participants, an independent association of ambulatory HR with subclinical cerebrovascular disease identified from white matter hyperintensity volume was found for night-time HR but not for daytime HR [10]. In the Renis-FU study, HR was a significant predictor of rapid glomerular filtration rate decline measured 5 years later [11]. In both the baseline and fully adjusted models the closest association was found for asleep HR. Thus, alike ambulatory blood pressure, ambulatory HR seems to be more representative of the 24-hour hemodynamic load on the vascular system than office HR. Average ambulatory HR is less influenced by environmental stimuli that can affect office HR measurement and reflects the global burden exerted on the cardiovascular system [1]. In addition, ambulatory HR has better reproducibility than office HR, as shown by our results in over 800 HARVEST participants who performed two ambulatory blood pressure and HR monitorings 3 months apart [12]. Mean change and standard deviation were smaller for the ambulatory HR than office HR attesting to better reproducibility of ambulatory HR.

High HR affects the vascular wall by tensile stress and by turbulence of the blood flow [2]. The blood pressure-related tensile stress induces vascular stiffness whereas the low shear component of turbulence favors the development of atherosclerotic plaques. Increased frequency of heartbeats exposes the arteries to larger cumulative stress. Consequently, people with tachycardia are bound to develop premature and widespread vascular damage. Previous research has shown that the hemodynamic forces related to increased HR may play a crucial role in coronary plaque disruption [2]. High HR and the increased sympathetic tone underlying tachycardia can also favor the occurrence of ventricular arrhythmias and precipitate ventricular fibrillation and sudden death. The better prognostic capacity of asleep HR compared to awake HR is likely due to night-time HR being less affected by several confounders related to individual daily life behaviors that may greatly differ from individual to individual. In particular, physical activity which has a large influence on daytime HR may vary from subject to subject and within the same subject when ambulatory recording is repeated.

One main issue with HR as a risk factor is how tachycardia should be defined. Based on published evidence, the European Society of Hypertension as well as other scientific societies identified the 80 bpm value as the cut point between normal and high office resting HR [13]. Obviously, the problem is even more complex for ambulatory HR as less prognostic information is available. Within the frame of the ABP-International study, we identified the lower limit of the upper quintile for HR measured in hypertensive patients, which could be taken as the upper normal limit [7]. The value (85 bpm) was the same for office and daytime HR, was lower for 24-hour HR (81 bpm), and as expected was much lower for asleep HR (73 bpm). The asleep HR level is very similar to the cutoff value we obtained from the ROC analysis for the prediction of cardiovascular events in the same study (73.6 bpm). Obviously, this is only a suggestion that needs confirmation from other large studies.

In conclusion, ambulatory HR is an important risk factor for cardiovascular disease and mortality in patients with hypertension. It provides prognostic information on top of office HR. It has better reproducibility than office HR. Among the ambulatory sub-periods, night-time HR seems to have the best prognostic capacity. Thus we think that, when available, ambulatory HR should be included in the risk stratification of the hypertensive patient.

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