Commentary: Hypertension Phenotypes: The Many Faces of a Silent Killer

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Introduction

Hypertension is a powerful independent risk factor for cardiovascular morbidity and mortality as well as all-cause death. It is known colloquially as the silent killer because it can be present in apparently healthy persons for several years without causing even minor symptoms.[1] The only way to detect and diagnose hypertension is to measure accurately the systolic and diastolic blood pressure (BP) levels in accordance with established guidelines. Recent advances suggest that *where* (home or clinic), *when* (day-time or night-time), and *how* BP measurements are taken (casual or 24-hour ambulatory) make an important difference.[2] Additionally, whether BP measurements are automated (and thus, unattended) or performed by the doctor, nurse, or other clinician, makes an significant difference.[2] Most importantly, hypertension detected and confirmed in one setting but never at other settings has noteworthy implications for diagnosis, risk stratification, treatment strategies, and long-term prognosis.[3]

The Many Faces of Hypertension

An estimated 10%-40% of patients not receiving antihypertensive medications may have normal BP in the clinic or doctor's office but out-of-office measurements that indicate BP in the hypertensive range.[4] These patients have masked hypertension and, compared with true normotensive persons, have more than a 3-fold increased risk of composite cardiovascular endpoint and a 2-fold increased risk of stroke.[5] Kawano et al have identified three subtypes of masked hypertension to include a "morning surge" hypertension, day-time or "worksite" hypertension,

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and a night-time or "nocturnal non-dipper" masked hypertension.[6] These subtypes and their clinical presentations have important implications for hypertension treatment and control.

In the reverse scenario of white-coat hypertension where patients have normal BP levels in out-of-office settings but hypertension on clinic measurements, the increased risk of cardiovascular disease and total mortality may be as high as 38% and 20%, respectively, in untreated patients compared with true normotensives.[7] However, the cardiovascular risk of untreated white-coat hypertension, in the absence of target organ damage, may not be significantly different from that of true normotensive persons. Mancia et al[3] also showed that the incidence and risk of cardiovascular and all-cause mortality were not significantly different from those of true normotensive persons if both 24-hour ambulatory and home BP measurements were normal.[3] However, discordant home and 24-hour ambulatory findings in white-coat hypertension were associated with significantly increased cardiovascular and all-cause mortality, as much as a 3-fold and 60% greater risk, respectively, in comparison with true normotensive persons.[3]

Beyond white-coat and masked hypertension, there are other hypertension phenotypes defined by the pattern of nocturnal BP dipping. On average, nocturnal BP is about 15% lower than day-time BP; thus, a failure of the BP to "dip" by at least 10% is considered "non-dipping." The nocturnal blood pressure dipping pattern adds important independent prognostic information for cardiovascular mortality and complications.[8] For example, in a large meta-analysis of individual data from 3,468 adult patients participating in four prospective studies, Fagard et al demonstrated that the dipping pattern and the night–day BP ratio independently predicted mortality and adverse cardiovascular outcomes.[8] In fact, the researchers showed that reverse dippers, non-dippers, and extreme dippers could be distinguished from the normal dipper phenotype among hypertensive patients and that these categories have prognostic value.[8]

Leveraging Phenotypes for Precision Health

The evidence now suggests that at least a dozen different phenotypes in primary hypertension can be identified using the combination of office or clinic BP, home BP, ambulatory daytime BP, ambulatory night-time BP, and the presence or absence of a normal nocturnal BP dipping. Despite these different phenotypes of hypertension, we tend to view patients with primary hypertension as a homogenous group. We also typically base long-term treatment strategies predominantly on the clinician-measured office BP although we have compelling evidence showing superiority of unattended clinic BP and out-of-office ambulatory BP measurements.[2]

We now have the opportunity to refine risk stratification and introduce an element of precision in our management of primary hypertension by tailoring pharmacologic, lifestyle, and behavioral intervention to the context and specific phenotype. However, we need research evidence to inform such a practice and also demonstrate superior outcomes from such a management strategy. We also need a better understanding of the social, environmental, physiological, genomic, and epigenomic determinants and drivers of these myriad phenotypes. This is why the article by Spatz et al[9] in this issue of *Ethnicity & Disease* is timely and a step in the right direction.

The ECHORN Study

With study sites in Puerto Rico, the U.S. Virgin Islands, Trinidad and Tobago, and Barbados, the Eastern Caribbean Health Outcomes Research Network Cohort (ECHORN) Study is well set up to prospectively explore the contextual factors associated with high-risk BP patterns detected on 24-hour ambulatory BP measurements in this population with a high burden of hypertension and cardiovascular diseases.[9] The primary objective of ECHORN is to identify phenotypes of hypertension based on the contextual factors associated with high-risk BP patterns. Their core measurements for this task include unattended automated clinic BP and 24-hour ambulatory BP with sleep and awake BP values and assessment of dipping status.[9]

The ECHORN Study's specific interest is in the contextual factors that characterize and influence sustained hypertension, masked hypertension, and nocturnal non-dipping hypertension. In addition to determining the epidemiology of these phenotypes in this population, the study hopes to leverage the anthropometric, laboratory, and self-reported survey data captured as part of the larger ECHORN Wave 2 assessments.[9] The study's

researchers will invite first-degree relatives aged <40 years and without prior diagnosis of hypertension to participate. Thus, the researchers will have an opportunity to assess genetic components of identified contextual factors. The study hopes to incorporate the comprehensive data collected in tools and applications "that capture the most relevant contextual factors influencing high-risk BP patterns," which can then be used to facilitate "a more precision-based approach to the prevention, detection, and control of hypertension."[9]

Opportunities for Advancing the Field

As designed, the ECHORN Study has a tremendous opportunity to advance the field by helping tease out the important social, environmental, biological, and contextual factors associated with different hypertension phenotypes in the Eastern Caribbean population. The study findings are likely to contribute significantly to efforts to refine strategies for detection, evaluation, treatment, and control of hypertension phenotypes. Most importantly, they are likely to be invaluable in our current era of precision medicine as we strive to deliver the right type of treatment for the right patient at the right time and with the right outcomes.

Conclusions

The time has come to recognize the many faces of primary hypertension. These phenotypes have important implications for clinical decision-making regarding risk stratification, prevention, treatment, and control of hypertension. However, this recognition cannot be made using our traditional reliance on the clinician-measured office or clinic BP alone. The evidence is now compelling that unattended, automated BP measurements are superior to doctor- or nurse-measured BP. Out-of-office BP measurements, comprising home BP or 24-hour ambulatory BP measurements, provide the necessary accompaniment to the office BP for diagnosing WCH, masked hypertension, and nocturnal hypertension phenotypes. We now know that several subtypes exist within these broad categories of phenotypes and that each has implications for clinical practice and research. We lack the full breadth of social, environmental, behavioral, lifestyle, contextual, and hereditary factors that characterize these phenotypes for different racial, ethnic, and ancestry populations. It is in this regard that the ECHORN Study of the Eastern Caribbean community provides exciting opportunities for discovery.

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While we wait for results from this and other research studies exploring the mechanistic underpinnings and contextual drivers of hypertension phenotypes as a way to advance more personalized approaches for hypertension treatment and control in this era of precision medicine, we should take steps to use our current strategies to treat and control hypertension worldwide. We already have safe and effective interventions and protocols to achieve 80%-90% hypertension control rates; however, we fall far short of this target in the United States and worldwide. We must redouble our efforts in raising awareness about the prevention, treatment, and control of hypertension and supporting the implementation, scale-up, and spread of the proven strategies we already have.

Conflict of Interest Disclosure
None

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The views expressed in this article are those of the author and do not necessarily represent the views of the National Heart, Lung and Blood Institute, the National Institutes of Health, or the United States Department of Health and Human Services.

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