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The Complexities of Hypertension: One Disease or Many?

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In 1905 Nikolai Korotkoff presented his seminal work on the utilization of auscultation to measure blood pressure (BP), a breakthrough that would ultimately allow for universal, routine noninvasive measurement of BP and screening for hypertension.¹ That same year, an editorial in the *British Medical Journal* provided a cautionary view on BP measurement-

“There is a certain risk that the multiplication of instruments tends to pauperize the senses and to weaken their clinical acuity; even the sphygmograph is mainly used nowadays for the purposes of demonstration or of making a permanent record than for what it can tell us in diagnosis or prognosis.”²

Was the author of this commentary cynical or prescient? Would scientists and clinicians utilize this newfound ability to measure BP routinely to its fullest extent? Or would BP measurement lead to the application of heuristic diagnostic and treatment approaches while ignoring the underlying pathology?

On one hand, our knowledge of hypertension has exploded in the century since Korotkoff's publication. Researchers have unraveled a number of the physiological processes associated with hypertension, including the interplay between the kidneys, vasculature, and nervous system. In addition, large epidemiological studies have demonstrated clear associations between elevated systolic BP (SBP), diastolic BP (DBP)s, and pulse pressure and subsequent damage to the heart, brain and kidneys. Closing the loop, multiple clinical trials have shown that successful control of blood pressure can effectively reduce the risk of stroke, heart attack, and chronic kidney disease.

Despite this progress, our understanding of how to use SBP, DBP, and pulse pressure for diagnosis, prognosis and treatment remains incomplete. While the sphygmomanometer may provide useful prognostic data, our clinical approach to hypertension has been guided primarily by its numerical measurements rather than the underlying physiology. There is little doubt that there are differences between an adult with isolated systolic hypertension, isolated diastolic hypertension, or combined systolic and diastolic hypertension, yet current guidelines treat all of these entities the same way. In reality, the clinical entity of “hypertension” may be an artificially homogenized constellation of diseases with different incidence rates, prognostic implications, and pathologic underpinnings.

In this addition of *JAMA Cardiology*, Yano and colleagues use data from the CARDIA study to demonstrate that the prognostic information conferred by SBP and DBP may vary

considerably by both race and age.³ These differences have important implications for the performance of risk models to identify high-risk adults for cardiovascular disease (CVD) prevention. Unfortunately, the majority of clinical trials and epidemiologic studies of hypertension have included mostly older white populations. As such, racial differences in the link between BP and CVD risk will lead to risk models and treatment paradigms that under-perform in minority populations.

Yet the biologic reasons for these differences are mostly speculative. Some of the racial differences in the observed prognostic implications of SBP and DBP may reflect differences in the prevalence of different hypertensive disease states in blacks and whites. But if the magnitude of risk conferred by elevated SBP and DBP truly varies by race, as suggested by this manuscript, then this phenomenon cannot be explained by differences in disease prevalence alone. Genome wide association studies helped unravel racial differences in chronic kidney disease through *APOL 1*, but to date have not found a specific genetic link underlying racial disparities in hypertension.⁴ While many have implicated psychosocial and environmental factors,⁵ the lack of a “silver bullet” found in the genome may be due to the complex nature of the interplay between blood pressure, the environment, and cardiovascular disease.

In this study, blacks had a two-fold increase in the risk of premature CVD compared with whites, as well as higher BP at younger ages. How elevations in BP lead to atherosclerosis over time is not fully understood. Do slight elevations in BP in early adulthood cause future disease, or is BP acting as a marker for underlying early endothelial dysfunction or premature atherosclerosis? Do black and white adults truly differ in their physiologic response to elevated BP? Or is race a surrogate for differences in the prevalence of other causal factors in the pathway between BP and atherosclerosis?

Filling these critical gaps in our understanding of BP will require a reconciliation between our current knowledge of hypertension epidemiology and physiology. To begin, our classification of what is a ‘normal’ BP may need refinement. In Yano’s et al study from CARDIA³, blood pressure at a young age was linked with CVD risk up to 25 years later. Notably, the vast majority of both black and white adults did not have levels of SBP or DBP that would typically be classified as “hypertensive”. Long-term interventional clinical trials are needed to test whether treatment of these “pre-hypertensive” levels of BP in young adults can reduce the long-term risk of CVD.

Over the past 100 years, we have learned much about hypertension and its treatment. Studies such as the current report by Yano and colleagues³ demonstrate we have much left to discover. Several things are clear. First, hypertension is not likely to be one disease. Next, the risk of elevated SBP and DBP appear to be altered by race and age. Third, even low levels of “elevated” BP appear associated with future harm. As we move forward, the future of personalized medicine will require a deeper understanding of the physiology behind hypertension, with the ultimate goal of individualized prognostic and treatment approaches.

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