HHS Public Access

Author manuscript

Circ Res. Author manuscript; available in PMC 2020 March 29.

Published in final edited form as:

Circ Res. 2019 March 29; 124(7): 987–989. doi:10.1161/CIRCRESAHA.119.314403.

Precision Medicine: A New Paradigm for Diagnosis and Management of Hypertension?

Joseph Loscalzo

Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Keywords

genomics; network medicine; systems pharmacology

Hypertension is a disorder with significant global impact. With an overall prevalence of ~40% in adults age 25 or older, hypertension accounts for 7.5 million deaths, or 12.8% of total global deaths annually. While the diagnosis and treatment of hypertension are seemingly straightforward, the lack of control is commonplace, with ~40% of treated patients achieving blood pressure targets in the US (1). The reasons for failure to treat elevated blood pressure effectively are multifactorial and include drug intolerance, lack of adherence owing to the absence of symptoms or cost of drugs, physician inertia, and the mechanistic imprecision with which drug classes are chosen. Equally important is the fact that (essential) hypertension is an excessively inclusive phenotype that oversimplifies complex biology and derivative physiology. To use a somewhat hyperbolic comparison, the diagnosis of essential hypertension is as uninformative and potentially therapeutically misleading as would be an overly inclusive diagnosis of 'tachycardia' that fails to distinguish ventricular tachycardia from atrial fibrillation with rapid ventricular response. It should be no surprise, therefore, to recognize that the majority of patients are not well-served by current diagnostic and therapeutic paradigms for hypertension. Clearly, we need more nuanced phenotyping linked to genetically determined subgroup mechanisms that offer more specific, precise therapies to achieve optimal control of blood pressure and optimal morbidity and mortality benefit.

Interestingly, hypertension is among the first diseases to which precision phenotyping was applied. Laragh emphasized high versus low renin subgroups of essential hypertensives over 40 years ago (2), with implications for later-developed targeted therapies. Similarly, in the contemporary era of modern genomics, hypertension was among the first diseases to which genotyping was applied for characterization of subgroups, with a focus on the angiotensin-converting enzyme (*ACE*) gene indel subtypes (3,4). While neither of these efforts led to effective precision therapies, they paved the way for a growing number of similar studies.

For inquiries, contact: Joseph Loscalzo, MD, PhD, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, jloscalzo@rics.bwh.harvard.edu.

Disclosure: The author is a cofounder of Scipher Medicine, Inc., which utilizes molecular network approaches for precision diagnostics and therapeutics.

Early in the current era, leading geneticists in the field believed that one strategy for precision genotyping involves exploring the genetic basis of rare, largely monogenic variants that cause hypertension. These investigators argued that variants in these genes with lesser adverse effects on gene product function might alone or together conspire to promote less severe and more prevalent hypertension than the monogenic forms. While such studies have provided insight into causes and specific treatments for these monogenic forms of heritable hypertension (e.g., Liddle's syndrome, pseudohypoaldosteronism) (5), the findings have not translated into a deeper understanding of potentially remediable subgroups of essential hypertension. In part, this shortcoming is a reflection of both the genetic complexity of essential hypertension and the phenotypic diversity of the disease(s).

The field of hypertension research has been informed by well characterized animal models of the disease for many years. Knowledge of the genetics of hypertension in these animal models set the stage for the subsequent human population studies, and partly informed their interpretation (6). Genome-wide association studies (GWAS) of hypertension are among the most abundant GWAS to date. While some of the early studies suffered from inadvertent inclusion of hypertensives in the control arm and, therefore, provided limited useful information, better designed more recent trials (7) have been quite revealing of the genomic complexity of the disease. The recent study by Warren and colleagues (2017) of >140,000 unrelated individuals, for example, identified 107 loci linked to the phenotype. By exploring the tissue-specific expression of the annotated genes linked to the loci and the pathways within which they function (when known), these investigators developed a genetic risk score based on the polygenotype, and validated it in an independent cohort as predictive of the development of hypertension. Other meta-analyses of large population GWAS bring the total number of loci to 120 (8).

Notwithstanding the extraordinary wealth of genetic information that has evolved from these population studies, the associated loci together account for not more than 3.5% of heritability of this complex trait (8). Multiple reasons explain the 'missing heritability' of hypertension, including dietary factors and lifestyle, stress, microbiome effects, and epigenetics. Equally important, however, is epistasis or genetic interactions, which can lead to greater than additive contributions to the trait. Given the large number of loci, the likelihood that any population study would have a sufficient number of individuals with at least pairs (let alone greater numbers) of potentially interacting loci is nil. Thus, different approaches are needed to address this potentially important mechanism of pathobiology.

The major problem with genetic association studies is that by their typical (feasible) design, they can only seek evidence for association between a single locus and a trait, even for highly prevalent pathophenotypes. Complex traits are caused not only by multiple loci, but also likely influenced by interactions between the gene products governed by these loci. Our work in network medicine has focused on the use of molecular interaction networks as a means to gain insight into pathways influenced by multiple genetic loci. We do so because studying simple loci-trait associations in complex phenotypes is as short-sighted as attempting to build a car engine by consulting a list of its parts without knowledge of the assembly diagram. Molecular interaction networks (interactomes) provide the information needed to identify interactions and their potential consequences for function. We have

applied this approach using the comprehensive physical interactome (all ascertainable protein-protein interactions in the cell) as a template, to which we map genes or gene products that have been associated with a pathophenotype. Doing so leads to the identification of discrete subnetworks within the comprehensive interactome that are specific for each disease—the disease module (9). Genetic variants can be mapped to the disease module to create an individual's disease module or 'reticulotype' (derived from the Latin term for network). This reticulotype can then be explored for relevant pathways within which variants operate to create abnormal module function. In our original paper on this concept (9), we applied these principles to type 2 diabetes mellitus, a complex trait to which ~200 genetic loci have been linked. The great majority of these loci have very small effect sizes (although they each have highly significant genome-wide significance). When we mapped these loci to the type 2 diabetes disease module in the interactome *ad seriatim*, we found that several created a clustering of associated binding partners that identified novel pathways and targets not previously recognized. These clusters were highly statistically significant (by z-score for clustering), provided the insight needed to address functional allelic interactions, and informed unique mechanisms and potential drug targets for the pathophenotype (9). A key to the benefit of the use of the interactome network in this analysis of epistasis is that it provides the 'missing links' that connect disease-associated loci to one another, as the network is created from comprehensive, unbiased physical association studies (e.g., yeast 2-hybrid screens). Network analyses have begun to be applied to hypertension, but largely in animal models, and not yet using physical interactome networks (6).

Of course, these genomic and network medicine analyses of hypertensive populations must be met with improved, deeper phenotyping than has typically been utilized. The fact that the definition of hypertension has been revised again [cf. Joint National Committee 8 Hypertension Guidelines (10)] based solely on blood pressure argues for a more precise definition of hypertensive phenotypes. These phenotyping efforts can include endophenotyping—i.e., phenotyping of intermediate phenotypes linked to hypertension—such as metabolic (11) and physiologic (including the use of mobile technologies) (12), as well as more precise phenotyping of the hypertension *per se*, which can include systolic, diastolic, and pulse pressure; nocturnal hypertension; 24-hour blood pressure patterns; arterial waveform; vascular stiffness; mean pressure variability throughout the day; 'white coat' hypertension; etc. These phenotypic and endophenotypic parameters can then be used to create phenotype networks (13,14) that can be analyzed to eliminate collinear parameters and effectively characterize the subgroup with a minimal number of effective elements. Machine learning strategies can, of course, also be helpful in this instance. Mapping the detailed, networked phenotypes to the molecular reticulotypes can then provide insight into predictive subgroups, redefining the diseases we call hypertension for prognostic and therapeutic benefit (15).

In my view, the question posed in the title of this piece can be answered in the affirmative. It is not *whether* we have the tools to achieve precision medicine goals for the diagnosis and treatment of hypertension, but *when* we can hope to do so. In contrast to rare diseases (including malignancies), it is unlikely that we will develop or need to develop personalized, in contrast to precision, medicine strategies for optimal diagnosis and treatment. Reasonably

sized subgroups with distinctive network-based targets and distinctive network-based phenotypes can serve as the basis for the future of precision medicine for hypertension, a future that, in my view, is rich with promise.

Acknowledgements:

The author wishes to thank Drs. Jane Leopold and Brad Maron for helpful comments, and Stephanie Tribuna for expert technical assistance. This work was supported in part by NIH grants HL61795, HG007690, GM107618, and HL119145.

References

1. Qamar A, Braunwald E. Treatment of hypertension. JAMA 2018;320:1751–1752. [PubMed: 30398610]
2. Brunner HR, Sealey JE, Laragh JH. Renin subgroups in essential hypertension. Further analysis of their pathophysiological and epidemiological characteristics. Circ Res 1973;32 (Suppl 1):99–105.
3. Nara Y, Nabika T, Ikeda K, Sawamura M, Endo J, Yamori Y. Blood pressure cosegregates with a microsatellite of angiotensin I converting enzyme (ACE) in F2 generation from a cross between original normotensive Wistar-Kyoto (WKY) and stroke-prone spontaneously hypertensive rat (SHRSP). Biochem Biophys Res Commun 1991;181:941–946. [PubMed: 1662504]
4. Zee RY, Lou YK, Griffiths LR, Morris BJ. Association of a polymorphism of the angiotensin I-converting enzyme gene with essential hypertension. Biochem Biophys Res Commun 1992;184:9–15. [PubMed: 1314601]
5. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001;104:545–556. [PubMed: 11239411]
6. Padmanabhan S, Joe B. Towards precision medicine for hypertension: a review of genomic, epigenomic, and microbiomic effects on blood pressure in experimental rat models and humans. Physiol Rev 2017;97:1469–1528. [PubMed: 28931564]
7. Warren HR for the UK Biobank CardioMetabolic Consortium BP Working Group. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. Nat Genet 2017;49:403–415. [PubMed: 28135244]
8. Dominiczak A, Delles C, Padmanabhan S. Genomics and precision medicine for clinicians and scientists in hypertension. Hypertension 2017;69:e10–e13. [PubMed: 28193712]
9. Menche J, Sharma A, Kitsak M, Ghiassian SD, Vidal M, Loscalzo J, Barabasi AL. Disease networks: uncovering disease-disease relationships through the incomplete interactome. Science 2015;347:1257601. [PubMed: 25700523]
10. Cifu AS, Davis AM. Prevention, detection, evaluation, and management of high blood pressure in adults. JAMA 2017;318:2132–2134. [PubMed: 29159416]
11. Tzoulaki I, Iliou A, Mikros E, Elliott P. An overview of metabolic phenotyping in blood pressure research. Curr Hypertens Rep 2018;20:78. [PubMed: 29992526]
12. Akintunde A, Nondi J, Gogo K, Jones ESW, Rayner BL, Hackam DG, Spence JD. Physiological phenotyping for personalized therapy of uncontrolled hypertension in Africa. Am J Hypertens 2017;30:923–930. [PubMed: 28472315]
13. Chu JH, Hersh CP, Castaldi PJ, Cho MH, Raby BA, Laird N, Bowler R, Rennard S, Loscalzo J, Quakenbush J, Silverman EK. Analyzing networks of phenotypes in complex diseases: methodology and applications in COPD. BMC Syst Biol 2014; 8:78. [PubMed: 24964944]
14. Oldham WM, Oliveira RKF, Wang RS, Opotowsky AR, Rubins DM, Hainer J, Wertheim BM, Alba GA, Choudhary G, Tornyos A, MacRae CA, Loscalzo J, Leopold JA, Waxman AB, Olschewski H, Kovacs G, Systrom DM, Maron BA. Network analysis to risk stratify patients with exercise intolerance. Circ Res 2018;122:864–876. [PubMed: 29437835]
15. Zhou X, Lei L, Liu J, Halu A, Zhang Y, Li B, Guo Z, Liu G, Sun C, Loscalzo J, Sharma A, Wang Z. A systems approach to refine disease taxonomy by integrating phenotypic and molecular networks. EBioMedicine 2018; pii:S2352-3964(18):30123-3.