Invited Commentary

Long-term BP variability: open questions in clinical practice

High blood pressure (BP), in terms of arterial BP absolute values (mmHg), is a mainstay of cardiovascular risk and an unquestionable target for pharmacological and nonpharmacological therapeutic strategies aimed at reducing the related burden of disease. Arterial BP absolute values are usually averaged from multiple measurements and, according to the setting where BP is measured, different thresholds define the diagnosis of hypertension. Averaging BP accounts for the phenomenon of BP variability, which constitutes an additional feature of BP phenotype. However, the prognostic importance of mean BP is as solid as the clinical significance of its variability is uncertain [1].

In fact, despite reflecting the interplay among the same biological/intrinsic determinants as of mean BP, including neurohormonal, humoral, metabolic, anatomic, environmental, and genetic factors, the definition and clinical meaning of BP variability remain controversial [1]. The impact of external modifiers of the biological determinants of BP profile over time (i.e. medications use and compliance [2]), as well as methodological issues (optimal timing, measurement setting and procedure) have so far prevented the scientific community from coming to a shared definition of reference ranges for BP variability, with the only exception of day-to-night BP changes expressed by the phenomenon of "dipping" [1].

BP variability is an expression of the degree of adaptation to, or compensation for, all sorts of challenges that might affect the cardiovascular system through BP regulation. Determining the extent to which such responses are normal requires the extrapolation of a variable that has to be independent (i.e. non collinear with mean BP; unbiased by external modifiers) and standardized (e.g. in terms of measurement technique, timing, and diagnostic threshold), which would also allow for the derivation of optimal (i.e. population-specific) target values. One of the issues raised with BP variability is indeed the uncertainty in the individual's BP status introduced by this variable, especially when based on measurements spread over time, as it is the case with long-term BP variability [3]. In parallel, however, this behavior might reflect the effect of biological events that the clinician might want to capture for a personalized assessment of the individual's cardiovascular risk profile.

In fact, BP variability might reflect a different susceptibility to common stressors and cardiometabolic risk factors. Also, the extent to which BP variability is impaired might depend on the pre-existing burden of disease. In other words, the residual functional reserve might determine qualitative and quantitative impairment in the individual's physiological BP changes. Thus, the same intra- and interindividual heterogeneity in BP variability that prevent the unanimous definition of its thresholds and targets might indeed carry the potential for personalized risk assessment.

It is typically the excessive BP variability that is associated with an increased cardiovascular risk. However, the evidence of a J-shaped association of BP variability with cardiovascular risk in some clinical settings (e.g. heart failure, high risk hypertension [4]) suggests that the inability to finely modulate BP changes might also occur in the opposite direction, i.e. as an inappropriately rigid BP profile. Thus, the inadequate compensation expressed in the J-shaped association with hard endpoints might be specific for some, but not all, risk categories. This might affect the generalizability of the prognostic implications of BP variability, while, in parallel, raising the possibility that 1) drugs affecting BP variability are not equally effective, with responsiveness being related to the pre-existing pathophysiological background; 2) customized cardiovascular risk models incorporating BP variability improve risk stratification.

Still, open questions remain concerning feasibility, reliability, and biological plausibility for cardiovascular risk customization of long-term BP variability. These issues require testing in specifically designed research in diversified clinical settings where traditional and novel/emerging cardiovascular risk factors are controlled for. Also, home BP measurements performed by guidelines might allow reduced between-visit delays than office BP measurements, and should be tested in future dedicated studies. Another criticism concerns how to express BP variability. Several indexes for long-term BP variability have been used so far, which contributes to convey uncertainty regarding the prognostic solidity of one or another measure, despite the existing correlation among different indexes suggesting a reasonable overlap of the attributable burden of cardiovascular risk. Strictly related to this point is the observation that the prognostic relevance of BP variability, when detected, could indeed reflect its dependency on absolute BP values, thus resulting only in an apparent determinant of cardiovascular risk, similarly to what was described for other clinical features of debated meaning [5]. Thus, a prerequisite for further research is also the evidence-based consensus on the index(es) used to define long-term BP variability, including the consistent use of indexes with the least confounding by
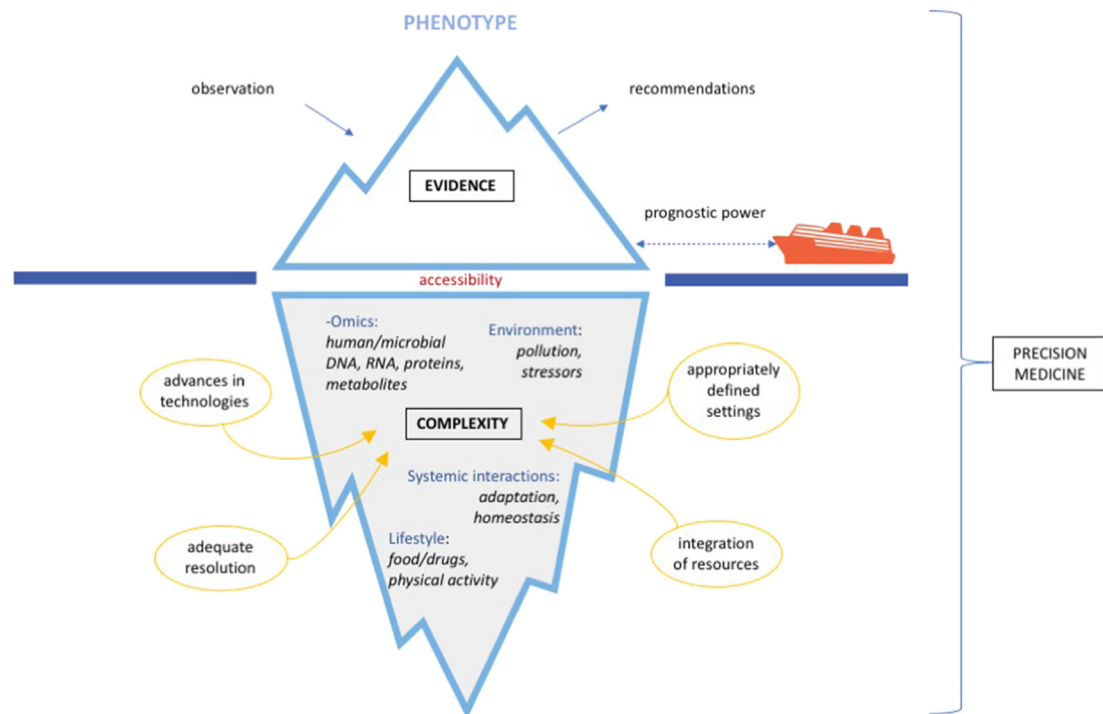
Fig. 1. Towards precision medicine: understanding the complexity behind the evidence. The individual phenotype reflects accessible features and complex traits. The more we learn about the determinants of this complexity, the more we will be able to prevent and manage the related diseases and conditions, as well as develop accurate prognostic models, in accordance with the mission of precision medicine. Technological progress and resource networks will provide high-resolution insights into the multiplicity of pathways, some of which are listed in figure, and the related dynamics that contribute to health and disease.

mean BP values (e.g. coefficient of variation, CoV, %; variability independent of the mean, VIM), the assessment as to whether population-specific features require the preferential use of a specific index, as well as determining whether conversion factors concerning the respective attributable risk might help dispel confusion arising from the multiplicity of measures so far developed.

With the above mentioned limitations clear in mind, it must be noted that several contributors to the individual's BP status are still undetermined. Cutting-edge research is striving to unravel the role of the immune system in cardiovascular pathology. Immunosenescence and chronic inflammation are two paradigmatic expressions of immune system changes with impact on the cardiovascular balance. The paraphysiological modifications in immunity occurring with age and the pathological events related to inappropriately persistent immune system activation during inflammatory diseases are emerging contributors to the observed high incidence of cardiovascular diseases, including impaired BP control, in these clinical settings [6,7]. Omics techniques will provide granular data to characterize the biological functions and dynamics of the cardiovascular system, which includes fathoming the reciprocal relations of foods and drugs with the human genome and the gut microbiome. Epigenetic profiling from human tissues with physiological relevance in BP regulation, e.g. resistance arterioles and nephron segments, coupled with in vivo studies assessing the functional role of epigenetic mediators, will help understand the mechanisms and dynamics underlying a complex trait like BP profile [8]. We will then be able to understand the finest specificity of each single contributor to BP profile, from aging to immunity, dysbiosis, circadian phenomena, and any other relevant factor that is only partially accessible at present [9]. A step forward would be, therefore, the implementation of precision medicine by identifying the most effective management strategies, from prevention to treatment, based on genetic, environmental, and lifestyle factors (Fig. 1).

No clinical application other than the field of research is currently approved for BP variability, but the evident, widespread interest in this topic is a prelude to the possibility of gaining wider insights into its determinants and clinical effects.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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