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Please cite this article as:

Zuoguang Wang and Xiaoyun Peng, Pathogenesis of essential hypertension: development of a 4-dimensional model. *Hypothesis* 2013, **11**(1): e3, doi:10.5779/hypothesis.v11i1.303

Pathogenesis of essential hypertension: development of a 4-dimensional model

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Received: 2013/06/06; Accepted: 2013/06/26;
Posted online: 2013/11/29

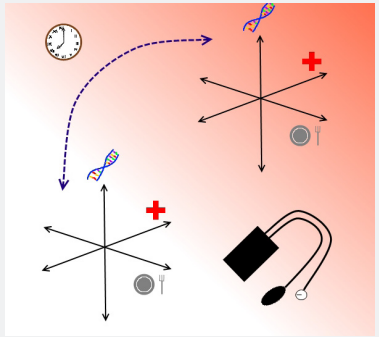

Illustration by Laura Isouthco

ABSTRACT Essential hypertension (EH) is regarded as a multifactorial and polygenic disease, and its underlying mechanism is very complex. A new model of EH pathogenesis was developed in the present work. This model is suitable for the study, diagnosis, treatment, and prevention of EH. It incorporates not only genetic and environmental factors, but also compensatory and time factors as the third and fourth types of factors that contribute to the development of EH. Compensatory factors are defined here as specific blood pressure (BP) regulators, the ability of the body to regulate BP, and the process of BP regulation. Time factors include the age of the patient and the duration of EH in that patient. Over time, genetic, environmental, compensatory, and time factors are dynamic. In this way, the development of EH is influenced by the interactions between these four factors. Herein, a 4-dimensional (4-D) model of EH pathogenesis is described, including primary approaches and technical considerations. The 4-D model will be useful in understanding the pathogenesis, diagnosis, treatment, and prevention of EH.

INTRODUCTION Essential hypertension (EH) is regarded as a multifactorial and polygenic disease. Formally, there are two kinds of important factors that can promote the development of EH: genetic and environmental factors[1]. Many clinical and experimental studies have indicated many possible mechanisms of EH, including increased activity of the sympathetic nervous system, overactivity of the renin-angiotensin aldosterone system (RAAS), dysfunction of the vascular endothelium, impaired platelet function, thrombogenesis, vascular smooth muscle and cardiac hypertrophy, altered angiogenesis, and microRNA (miRNA) deregulation[2]. However, these mechanisms only partially explain EH. The Human Genome Project, the International HapMap Project, and the development of molecular genetics have provided new enthusiasm for elucidating the genetic mechanisms underlying EH. However, although hundreds of hypertension-related genes have been found and some genome-wide association studies have produced interesting results, only 1% of blood pressure (BP) changes can be explained by genetic variation[3–5]. Environmental factors, such as stress and chronic high intake of dietary salt, have been found to be related to EH and there is a consensus among clinical and research scientists that they are important risk factors for EH. Neither genetic nor environmental factors can fully explain the pathogenesis of EH. The potential mechanism underlying the origin and development of EH origin remains unclear.

For these reasons, the present work proposes a new hypothesis that may give a clearer and more integrated explanation of EH. This hypothesis is based on the results of gene expression, transcription, metabolic, and protein studies, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[1], the achievements of physiology, pathophysiology, genetics, environmental sciences, system theory, and philosophy, and the observations made by the authors in their clinical practice and basic research into hypertension.

HYPOTHESIS It is hypothesized here that BP is regulated by three basic types of factors: environmental, genetic, and compensatory factors. These three types of factors change dynamically with the fourth factor: time. In this way, EH is influenced by the four factors and their interactions. The hypothesis can be expressed in the form of a 4-dimensional (4-D) model of EH pathogenesis, which is defined as follows: environmental and genetic factors act as the first two dimensions, compensatory factors are the third dimension, and time is the fourth dimension. At each point in time, BP is determined with respect to interactions among the environmental, genetic, and

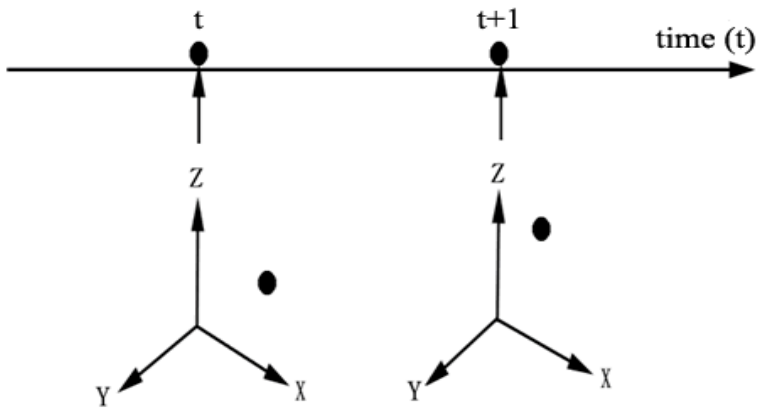

Figure 1 | The 4-dimensional model of pathogenesis of EH. *As time (t) passes, BP values change in the X-Y-Z space-time dimensions.*
X represents environmental factors, Y represents genetic factors, Z represents compensatory factors, t represents the time factor, and the black spot represents the BP value.
BP, blood pressure; EH, essential hypertension.

compensatory factors. Over time, BP changes. This model accurately reflects the actual BP maintenance and regulation observed in normotensive and hypertensive subjects (Figure 1).

Generally, environmental and genetic factors act on the human body to promote increases in BP, and compensatory factors mainly act as protective factors and counteract these mechanisms. Over time, if the compensatory factors are markedly stronger than the environmental and genetic factors, BP remains within normal limits (systolic BP [SBP] < 120 mmHg, diastolic BP [DBP] < 80 mmHg). If the compensatory factors are only slightly stronger than the environmental and genetic factors, BP increases to prehypertensive levels (120 mmHg ≤ SBP < 140 mmHg and/or 80 mmHg ≤ DBP < 90 mmHg). If the compensatory factors are weaker than the environmental and genetic factors, then BP becomes high (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg)[1]. The schema of EH pathogenesis is shown in Figure 2.

Supporting Arguments Traditionally, environmental and genetic factors have been considered the most important contributors to the development of EH. For this reason, these two types of factors have been studied broadly and in depth. However, in clinical practice, genetic and environmental risk factors do not absolutely predict the development of EH in young patients. For example, when BP increases, aldosterone and atrial natriuretic peptide (ANP) secretion increase in a compensatory manner[6,7]. These compensatory factors are very important in the maintenance of normal BP. Patient age and the course of EH can also affect the condition. During different stages of EH development and as a product of age, the risk factors, pathogenic factors, pathophysiological reflexes, and compensatory mechanisms vary widely[8-10]. These factors also affect BP. Unfortunately, however, these factors have not yet been adequately investigated and are not integrated into the prevailing understanding of the mechanism underlying EH. Therefore, a new theory integrating all these categories of factors affecting BP is discussed below.

ENVIRONMENTAL FACTORS: Stress, overweight, a high sodium and low potassium diet, being physically inactive, and exposure to toxins, pathogens, radiation, and chemicals are common environmental factors in the development of EH. Because these factors can affect BP, changes in these factors during the development of EH are important. Environmental factors may also change during the development of EH[11].

GENETIC FACTORS: The importance of genetic factors in the development of hypertension is indisputable. The primary DNA sequences of genes related to hypertension do not change between birth and death, but the expression of related genes does change in some cells and tissues[12]. For example, when an individual ages or progresses to a different stage of EH development, the expression of genetic factors that are directly and indirectly related to BP may change, including changes in endocrine response, cell repair mechanisms, and specific organ functions[13,14]. The underlying mechanism for changes in gene expression is mainly the regulation of gene expression. For example, epigenetic factors can regulate somatic angiotensin-converting enzyme by DNA methylation and histone acetylation[15]. 5-Methylcytosine, a well-known epigenetic marker, may be related with the control of BP[16]. These changes may be beneficial or harmful to the development of EH. In this way, genetic factors are important and dynamic during the development and progression of EH.

COMPENSATORY FACTORS: Compensatory mechanisms are very common in EH. Here, compensatory factors are defined as vasoactive factors that regulate BP, the ability of the human body to regulate BP, and the process of BP regulation[17–20]. For example, the concentration of angiotensin II (AngII), a vasoconstriction polypeptide, is increased in plasma, but that of ANP, a vasodilatory polypeptide, is also increased in plasma[21]. An increase in AngII may be part of the primary etiology of EH, but an increase in ANP secretion (or that of any other BP-lowering agent) may be part of a compensatory mechanism that helps to lower BP. Because ANP is a powerful vasodilator and a polypeptide hormone involved in the homeostatic control of body water, sodium, potassium, and adipose tissue, it can reduce the water, sodium, and adipose loads in the circulatory system, thereby reducing BP[22]. This regulation is a continuous part of the body's regulation of homeostasis[20]. The result of this regulatory process reflects the compensatory ability of the human body.

In fact, compensatory factors can be divided into direct and indirect categories.

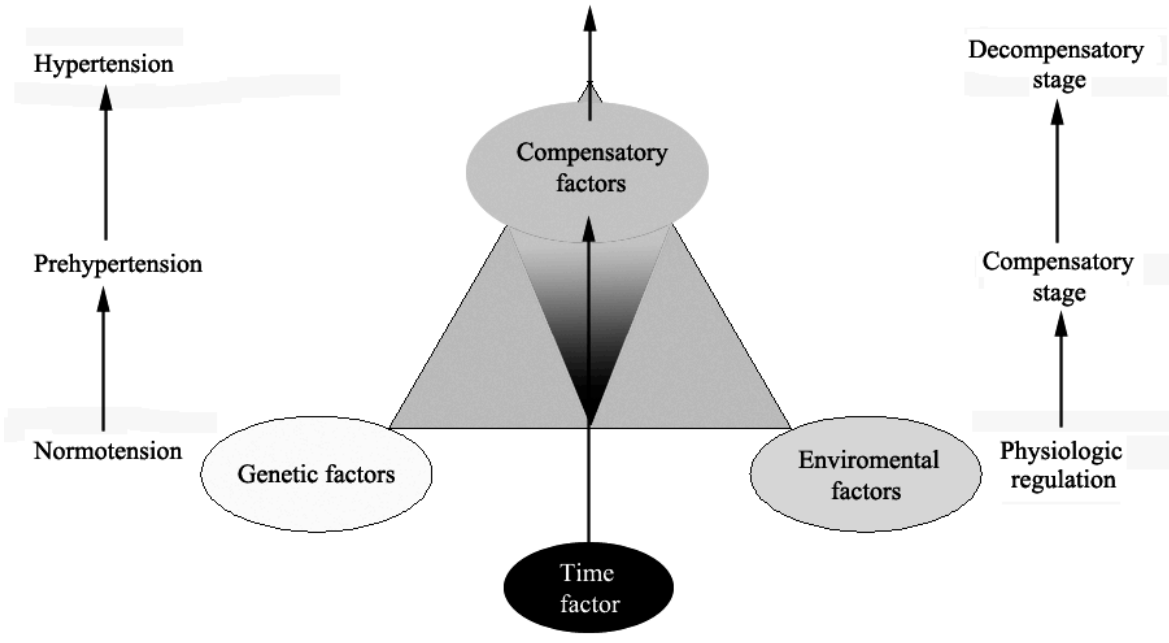

Figure 2 | The development and regulation of BP in patients with EH. Normotension, prehypertension, and hypertension represent three levels of EH development. Physiologic regulation, compensatory stage, and decompensatory stage represent the BP regulation process at different stages of EH development. Environmental factors and genetic factors are two high BP-promoting factors, while compensatory factors act mainly as BP-lowering factors. With an increase in promoting factors, compensatory factors also increase. When the human body can no longer compensate, EH may develop. Time factors dynamically record the process of EH development.
BP, blood pressure; EH, hypertension..

As noted above, ANP is a direct factor, and ANP hydrolase is an indirect factor. Some factors, such as endorphins, may be an unrelated factor caused by the stress of EH[23]. In the study of EH, not only the primary etiology of EH but also the compensatory factors and indirect compensatory factors should be identified. Only then will the real etiology of EH become discernible. Because compensatory factors are generated and changed in response to primary EH promoting factors, compensation is hysteretic and passive. This response paradigm and changes in compensatory factors over time aid the identification of them (compensatory factors).

Compensatory factors are not always beneficial to the human body. For example, when BP increases, the secretion of ANP also increases, and this decreases BP. Low BP can decrease the secretion of ANP. This is an example of a negative feedback loop (virtuous circle). However, increased BP may induce vascular smooth muscle cell proliferation, which can increase vessel stiffness and cause BP to increase further[24]. This is a positive feedback loop (vicious cycle). Unfortunately, in patients with EH, factors that promote primary hypertension always appear stronger than the compensatory factors. In this way, EH may originate from insufficient compensatory factors in affected patients. This can induce hypertension-related complications[25].

TIME FACTORS: Time is a necessary index for all factors. Time is also an unavoidable index in the development of diseases, including EH. During the onset phase, the effect of environmental, genetic, and compensatory factors on the development of EH and its complications are completely different from their effects during later stages. For example, a 40-year-old man with a 10-year history of hypertension may be subject to different factors from a 40-year-old man with a 1-year history of the disease and may have higher risk of cardiovascular disease[26]. The three types of factors also differ across different age groups. For example, young, middle-aged, and elderly people have very distinct compensatory abilities with respect to high BP[27–29]. Early-onset patients may have more pronounced exposure to environmental risks, more problematic gene expression, or weaker compensatory mechanisms than patients who do not suffer from EH until they are older. In this way, in our model, time was most commonly discussed in terms of patient age and duration of disease. Over time, environmental factors, genetic factors, and compensatory factors are dynamic. If time is not taken into account in the study of EH, the results will not reflect the true alterations in the human body. Unfortunately, however, almost all recent studies consider only patient age. A dynamic, time-sensitivity study of EH will be more valuable.

Interactions between different factors: Although the four factors noted above exist independently, they also interact[30]. First, environmental factors affect gene expression. Studies have found that drugs, chemicals, temperature, and light can determine which genes are turned on and off, thereby influencing the way an organism develops and functions. Hudson confirmed that diaminodiphenyl methane has a very specific role in maintaining transcriptional silence of

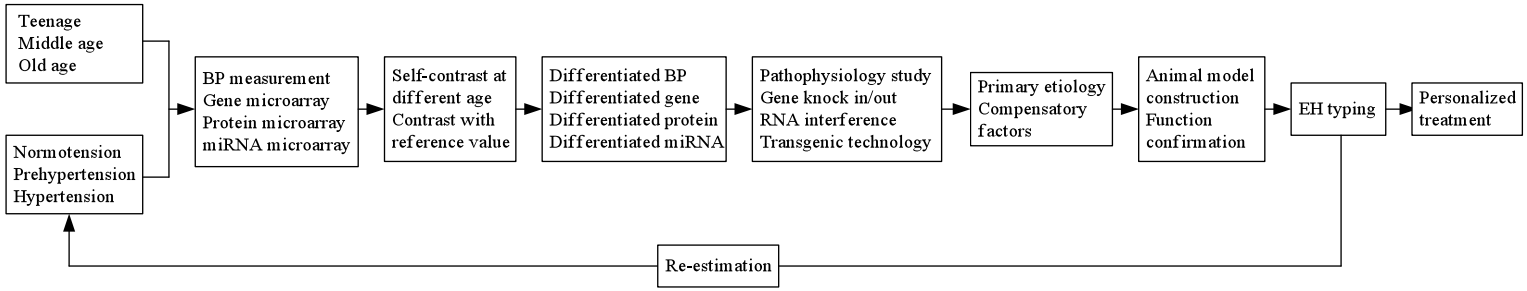

Figure 3 | The creation of the 4-dimensional model in the study of EH. The flow diagram shows the 4-dimensional model in the study of EH. Firstly, environmental, genetic, and compensatory factors are estimated in patients of different ages and at different stages of hypertension by measuring BP and conducting gene expression, miRNA, and protein array analysis. Secondly, after comparison to reference values from a normal population, the differentiated genes, miRNA, and proteins and changes in BP are analyzed. Thirdly, using pathophysiology, gene knock out and knock in, RNA interference and transgenic techniques, secondary factors and compensatory factors are rejected, and primary etiologies are identified. Fourthly, animal models and cytology research are used for further confirmation. Finally, the confirmed etiologies are used for EH typing. EH typing can be re-estimated by going back to the first step. After EH typing, personalized treatment may be possible.
BP, blood pressure; EH, essential hypertension.

transposable elements and that chemical inhibitors of DNA methylation can affect gene expression on a global level[31]. Second, genetic factors affect the susceptibility of the human body to environmental factors[32]. Third, compensatory ability is determined by genetic factors and also influenced by environmental factors and time[33]. Compensatory factors can also affect the ability of human beings to adapt to environmental factors and react to genetic factors, thereby impacting the development of EH. Because compensatory factors, environmental factors, and genetic factors change over time, time variables are extremely important in determining how the disease progresses and how long patients with EH live.

SIGNIFICANCE OF THE 4-D MODEL The 4-D model of EH pathogenesis proposed here is suitable for the clinical study, pathophysiology research, diagnosis, treatment, and prevention of EH in six principal ways.

First, this model may allow the redefinition of EH. Because the model addresses four factors, it can be used to explore the concept of EH more thoroughly than previous models. In this way, EH can be defined as a disease caused by genetic and environmental factors and resolved or partially resolved by the human body. When the promotive power exceeds the compensatory power for a sufficient period of time, EH will develop. EH is a chronic, progressive disease involving multiple systems and organs, particularly the cardiovascular system. This new understanding of EH gives a complete and clear description of the condition's origin, development, and related complications.

Second, this model can be used to change and improve the screening criteria for cases and controls in studies of EH in humans. For example, only participants of the same age and similar duration of EH (similar treatment if needed) may be selected. They are also expected to be older than 40 years of age. Failing to match participants by age and duration of disease in EH studies will yield inaccurate results. Other very important changes include stricter screening criteria and significantly enlarging sample size. In previous studies, sample sizes of 20,000 participants were thought to be large enough. However, even if there are only 10 genetic factors and 10 environmental factors that can result in EH, there are at least 1,046,529 [[C(10,1)+C(10,2)+.....+C(10,10)]×[C(10,1)+C(10,2)+.....+C(10,10)]]=1023×1023)] kinds of risk factor combinations for EH. Using the 4-D model, the number of risk factor combination will be very large. Therefore, although some genome-wide association studies have screened thousands of subjects[3,4], perhaps even those sample sizes are too small. Larger sample sizes and stricter criteria are urgently needed.

Third, in terms of pathogenesis, previous studies have considered only environmental and genetic factors. As noted above, compensatory factors and time are two very important determinants of EH development. If these two types of factors are not taken into consideration, many compensatory factors may be incorrectly identified as genetic or environmental in origin[34]. This may lead to incorrect conclusions regarding the specific pathogenesis and limit etiological investigations of EH. The 4-D model allows consideration of all three types of factors over time, and the primary causes (environmental or genetic) can be distinguished from secondary factors (compensatory factors). This will help to define and describe the pathogenesis of EH more clearly and accurately than other current systems.

Fourth, the 4-D model can facilitate diagnosis. Because the EH diagnosis system currently in use is based on indirect BP measurement, early diagnosis of EH is impossible. Although some single nucleotide polymorphism (SNP) gene arrays have been used in the genetic diagnosis of EH, this technique is limited due to the limited nature of the SNP

database and the scarcity of studies on SNPs related to EH[35–37]. However, the 4-D model allows dynamic estimation and detailed analysis of environmental, genetic, and compensatory factors. When combined with the early detection of dynamic changes in BP, it can be used for early diagnosis of EH.

Fifth, the 4-D model has great potential for improving EH treatment. Currently, the treatment of EH focuses on risk factor modification, antihypertensive drug administration, and target organ protection. All of the patients under treatment used hypertensive agents from one or more of the six categories without consideration for patient-specific etiology. In fact, the real cause of EH is unknown in these patients[38]. AngII type 1 receptor blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists are used for target organ protection. Under the direction of the 4-D model, patients of different ages, patients at different stages of EH, and patients with different EH etiologies can be differentiated, allowing the selection of appropriate drugs. The identification of the specific causes of EH may facilitate the discovery of new drugs suitable for antihypertensive treatment, making personalized EH treatment possible.

The sixth aspect of the 4-D model's usefulness is in the prevention of EH. The present prevention strategy mainly focuses on environmental factors and lifestyle modification in prehypertensive and early hypertensive patients[39,40]. During the development of EH, environmental, genetic, and compensatory factors all dynamically influence BP, and the prevention of EH must begin early and remain continuous. For example, the risk factors of adolescents should be assessed at regular intervals. If BP-related risk factors, and compensatory factors are significantly different from those of normal controls, EH prevention strategies should be implemented early and aggressively so that young, high-risk individuals may benefit. In this way, the 4-D model of EH prevention may allow preventative regimens to be started earlier and performed more completely than in the traditional model.

CREATION OF THE 4-D MODEL The definition and significance of the 4-D model during the development of EH are described above. The next step was to create a practically relevant 4-D model. In Figure 3, we describe the creation of the 4-D model. As shown, environmental, genetic, and compensatory factors were estimated in patients of different ages and at different stages of hypertension, by measuring BP, gene expression, miRNA, and protein array analysis[41]. After comparison to reference values from a normal population, the differentiated genes, miRNA, and proteins and changes in BP changes were analyzed. Then, using pathophysiology, gene knock out and knock in, RNA interference, and transgenic techniques, secondary causes and compensatory factors of EH were rejected, and primary causes were identified. Animal models and cytology research were used for further confirmation. Finally, the confirmed etiologies were used for EH typing. It can be re-estimated by going back to the first step. After EH typing, personalized treatment may be possible. In this way, studies on the subtyping, diagnosis, treatment, prevention, and pathogenesis of EH can be performed.

CONCLUSION The traditional study of EH has several limitations. Although many genes and environmental factors have been found to be related to EH, they were not found to be determinant. EH can also be caused by other, co-determinant factors. The currently established 4-D model theory integrates all of these factors. This makes this model valuable not only for the pathogenesis, diagnosis, treatment, and prevention of EH but also for drug development. According to the "common diseases, common variants" theory[42], only some genes mutate during the development of EH. It may be possible to study and type EH using 4-D model-directed studies. The realization of this model mainly relies on the establishment of a database containing BP and other related information including environmental, genetic, and compensatory factors of different age. Only after the normal reference values have been established, is the early identification of potential hypertensive patients possible. Although this paper describes a novel basic strategy for future EH studies, additional studies are still needed.**H**

ACKNOWLEDGEMENTS This work was supported by the National Natural Science Foundation of China (No.81270216, No.81370229) and the Beijing Natural Science Foundation (No.7102045, No.7133232, No.7120001). This paper was edited by Dr Jessica Cambensy, Dr Shih-Wen Lou, and Dr Michele Agnew of American Journal Experts and experts from LetPub.

CONFLICTS OF INTEREST Authors declare no conflicts of interest.

ABOUT THE AUTHORS Dr Zuoguang Wang has worked on clinical and experimental hypertension research for 24 years. He has been both a physician and a basic science researcher. He has published a total of 64 papers and one book, including 10 Scientific Citation Index (SCI) papers and three co-edited books. He is responsible for two projects from National Natural Science Foundation of China and one project from Beijing Natural Science Foundation and participates in 11 national and Beijing city research grants. Prof. Xiaoyun Peng has worked on biology and cardiac pharmacology for 21 years. She has published 21 papers, including two SCI papers, and has participated in five provincial funded projects.

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