Chapter 1

Introductory chapter: Essential Hypertension in the Twenty-First Century…What is Next?

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1. Introduction: historical concerns about blood pressure determination

The history of hypertension measurements begins in the late 1800s, with the introduction of the sphygmomanometer, an instrument to measure blood pressure with a noninvasive device.

At that time, some practitioners were still skeptical about the clinical importance of determining blood pressure. Others considered it as a valuable tool for diagnosis and began with early descriptions of the variability of blood pressure among individuals [1].

Additionally, the life insurance industry in the United States played also an important role in the recognition of an association between blood pressure level and cardiovascular morbidity and mortality. In the first half of the twentieth century, the use of the sphygmomanometer was indispensable in life insurance examinations because insurance companies required it for the applicants. The Actuarial Society of American published a report in 1939 about the relationship between blood pressure and mortality from cardiovascular and renal diseases. However, the clinical significance of high blood pressure during this time was not well understood, and essential hypertension was considered as a compensatory feature of blood pressure to ensure adequate perfusion of the target organs. This is the explanation why many clinicians were reluctant to treat high blood pressure because essential hypertension was considered a control mechanism to assure tissue perfusion, only to be controlled or regulated, even when there was increasing evidence of the association of cardiovascular disease and mortality with high blood pressure [2].

The two first clinical trials from the Veterans Administration Cooperative Studies evidenced the benefits of lowering blood pressure with antihypertensive treatment, published in 1967 and 1971, respectively. The design of both studies served as a prototype for future clinical trials. Furthermore, on a report in 1979, the Actuarial Society of American concluded that

mortality ratios rose with an increase in blood pressure in both men and women; they stated that overweight (35–45% above the average weight) increased mortality considerably in men with high blood pressure. Coronary disease, cerebral hemorrhage, left ventricular hypertrophy, and renal disease were among the causes of death identified, and mortality of these causes rose as blood pressure increased [2]. Since then, many studies showed that reduction in high blood pressure reduces cardiovascular morbidity and mortality for hypertension and served as evidence for early recommendations for antihypertensive therapy [3].

2. Epidemiologic transition: infectious diseases are replaced by cardiovascular diseases

During 1940s and 1950s, after World War II, the health priority became the control of infectious diseases, because they were the major contributors to morbidity and mortality at that time. As a consequence, the efforts in public health to control and prevent infectious diseases resulted in the decline in mortality rates and average life expectancy increase. During the twentieth century, an epidemiologic transition was evident in developed countries, in which infectious disease pandemics were replaced as a major cause of death by chronic degenerative diseases, such as cardiovascular diseases [4].

Since mortality rate for cardiovascular disease had been increasing progressively, the National Health Institute, in USA (now known as the National Heart, Lung, and Blood Institute) decided to conduct an ambitious project in 1948: the Framingham Heart Study. The researchers of the project recruited more than 5000 men and women who had not suffered symptoms of cardiovascular disease or had a cardiovascular event—heart attack or stroke, and analyzed them over a long period of time [5, 6]. As a prospective longitudinal epidemiologic study, its objective was to characterize the population subject to cardiovascular disease. The original cohort was followed up over decades, enrolling a second and a third generation to the original cohort. Since 1951, several articles were published based on research results of the Framingham Study, obtained by the careful monitoring of the study population, which led to the identification of the major coronary heart disease risk factors—high blood pressure, high cholesterol levels, smoking, obesity, diabetes, physical inactivity, closely related to other factors such as blood triglyceride and HDL cholesterol levels, age, gender, and psychosocial issues.

3. Essential hypertension: definition and etiology

Essential hypertension, also known as primary or idiopathic hypertension, is the presence of high blood pressure not explainable by secondary causes, representing 95% of all cases of high blood pressure. Secondary causes of hypertension are aldosteronism, renal disease, pheochromocytoma, hyperthyroidism, etc. [7].

Essential hypertension is a quantitative characteristic, defined by its strong positive correlation between blood pressure and risk of cerebral or cardiac, events and kidney disease. The etiology

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of essential hypertension is complex, and it is possible that multiple factors interact and produce hypertension. Furthermore, it has become notorious that a genetic susceptibility and the interaction of environmental factors, such as stress, diet, and physical activity play a relevant role in the pathogenesis of hypertension, as suggested in 1949 by Page in his mosaic theory to explain the possible mechanisms involved in the etiology of hypertension (**Figure 1**) [8]. The development of essential hypertension is composed of a primary process, in which vasoconstriction raises blood pressure initially, followed by a secondary amplifying process, in which the difference in blood pressure rises throughout life. This primary event can be in the perinatal and early postnatal life, a phenomenon known as 'intrauterine programming', important in long-term effects on the subsequent development of high blood pressure, with possible onset of hypertension during childhood and adolescence.

In developed countries, there is a probability of 90% of becoming hypertensive during the lifetime. Risk factors often cluster with other cardiovascular risk factors in individuals with an unhealthy lifestyle, including the sedentary lifestyle, smoking, stressful life of industrialized societies and Western diet patterns. Among dietary factors, it has been demonstrated that excessive salt intake, high alcohol consumption, low intake of potassium and calcium are related to hypertension. On the other hand, an increased consumption of polyunsaturated fatty acids of the omega-3 family has shown to have a hypotensive effect and reduces the cardiovascular risk.

Furthermore, blood pressure is affected by several environmental factors such as ambient temperature, air pollution, and noise. In addition, the repeated or prolonged exposure to these factors leads consequently to an increased sympathetic and adrenal activity [9]. Likewise, stress related situations, such as job strain, emotional distress, and social environment can cause hypertension through repeated blood pressure elevation and increased secretion of vasoconstrictive hormones.

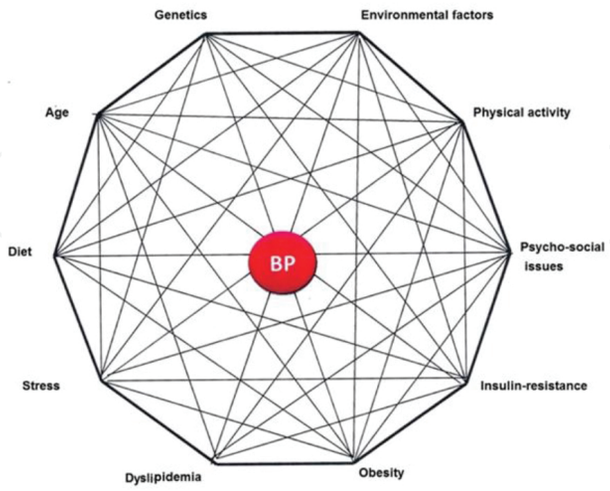

Figure 1. Interactions of factors in essential hypertension development, modified from the original Paige's mosaic theory of blood pressure regulation [8]. There is a circuitry of several factors interacting in an individual that may lead to the development of essential hypertension, such as genetic background, diet, physical activity, psychosocial factors, environmental factors, obesity, insulin resistance, dyslipidemia and stress.

Recognition of a genetic basis in hypertension is deduced from epidemiological and family studies, such as the Framingham Study [10]. Genetic alterations and polymorphisms in inherited 'essential' hypertension have also been identified. As a result, the individual response to the environmental factors mentioned above is variable, because the effect of an allelic variation of any gene depends on the environment in which the gene is expressed. In summary, it becomes clear that various factors contribute to blood pressure elevation in essential hypertension in susceptible individuals.

4. Twenty-first century challenges: genetic strategies and personalized medicine

Hypertension is a major contributor to cardiovascular disease, a leading cause of death in many countries. For this reason, there exists a commitment of many health organizations worldwide, to continue initiatives of research in hypertension. In the last twenty years, the use of experimental animal models for hypertension-related research has provided information in various aspects of the disease, which includes etiology, pathophysiology, complications, and treatment. In addition, comparative mapping techniques allow comparison of the syntenic genomic regions between rodents and the human genome. Recently, the identification of the role of cardiovascular genetic determinants of hypertension through linkage analyses and genome-wide scan studies permits a better understanding of the complex genetic architecture of the disease [11]. Numerous genes have been identified, including the genes from the renin-angiotensin-aldosterone system, the epithelial sodium channel, the adrenergic receptor, endogenous adducin, etc.

Furthermore, pharmacogenetics association studies in hypertensive patients are a useful tool helping to individualize therapy, by predicting patient response to a treatment, chosen to provide greatest clinical efficacy with the lowest risk of adverse effects.

5. Conclusion

During the twenty-first century, it has been a challenge to find the genetic etiology of human essential hypertension. Many studies on genetics and pharmacogenomics of hypertension have served as the basis, facilitating results of the role of candidate genes. However, as high blood pressure results from a complex interplay of diverse environmental and genetic factors, the replication of many studies has been problematic. The application of genetic data to the current therapeutic guidelines must be encouraged because provided evidence from several studies has not readily been translated into personalized medicine. The heterogeneity and complexity of the genetic network that in interaction with the environment controls the physiological mechanisms involved in blood pressure regulation has hampered the clinical application of animal genetic results to humans [12]. Additional discoveries in hypertension pharmacogenomics are expected to be obtained from genome-wide association studies. In

order to translate the findings of candidate gene studies and genome-wide association studies to the clinical practice, more efficient genetic testing, denser mapping techniques, full utilization of animal models and increased collaboration among research groups need to be improved.

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