• Literature Review •

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Blood Pressure Difference Between Genders and Its Biomedical Significance

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[KEY WORDS] Gender; Sex; Blood Pressure; Hypertension; Polygenic Disease

[ABSTRACT] The ever-increasing incidence of hypertension and the high death rate of cardiovascular diseases raise an issue of how to efficiently identify genes associated with the polygenic diseases of hypertension. Significant gender differences in hypertension have been recognized over one hundred years. Males have higher average values of blood pressure as well as higher incidence of hypertension as compared to females in many ethnic groups. Genes or genetic polymorphisms governing the higher normal value of blood pressure in males may be the susceptible factors of hypertension. Hormone related genes or imprinting genes are considered as involvement in the development of gender differences of normal blood pressure and hypertension. The gender differences in responding to pro-hypertensive or anti-hypertensive agents have clinical implications in clinical practice. Additionally, better understanding the molecular genetics of normal blood pressure differences between genders may yield the identification of genes associated with the development of hypertension and eventually benefit to the diagnosis and therapeutics of hypertension.

Blood pressure is a phenotypic trait regulated by multiple genes. One of the most important pathologic statuses related to blood pressure is hypertension. Except for secondary hypertension, primary hypertension is well-recognized as a polygenic disease[1]. Although the completion of The Human Genome Project has greatly accelerated the identification of genes causing many monogenic diseases, the cloning of genes associated with the primary hypertension is still a challenge in biomedical research[2]. We argue that the existence of blood pressure difference between genders[3-10] and the identical criteria[11] used for the diagnosis of hypertension may be one of the reasons that restrain the molecular genetic study of primary hypertension. This minireview revisits blood pressure differences between genders and discusses their implications in basic hypertension research and clinical practice related to hypertension.

1 Differences of blood pressure between genders

Although the criteria used for hypertension changes over time (Table 1), difference between genders has not been suggested officially[11]. Based on the identical diagnostic criteria used for both male and females, clinical observations demonstrated a 2-3 folds higher incidence of hypertension in males as compared to females in selected Chinese subpopulations[12, 13]. One debatable data is that the overall hypertension related death rate in males is not dramatically different from that in females, which may be at least in part related to the gender differences of normal blood pressure in addition to the longer life span of females. Similar to many other phenotypic traits such as hemoglobin contents, skeletal muscle strength, and body heights, the theoretical values of pressure in males that function physiologically may be higher than that of females. It is interesting that both experimental and clinical observation have reported significant differences between males and females[3-10, 14, 15]. In addition to the differences in physiological values between genders, Sõnz J et al demonstrated the gender specific responsiveness to nitric oxide antagonists of cyproterone acetate or flutamide in rats[15]. When the male rats were testectomized, the gender specific response was eliminated, which had a therapeutic implication.

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Table 1. Comparison of an used and an updated diagnosis criteria of hypertension

Category	Systolic(mmHg)	Diastolic(mmHg)
1978 old criteria		
Hypertension	⩾160	or ⩾95
2004 new criteria		
Normal	< 120	and < 80
Prehypertension	120~ 139	or 80~ 89
Hypertension		
Stage 1	140~ 159	or 90~ 99
Stage 2	⩾160	or ⩾100

We recently analyzed blood pressure values from individuals under regular physical examination. Significant differences between genders were observed in systolic and diastolic pressures measured during a regular physical examination in subgroups of undergraduates (Figure 1). Our data is consistent with many observations based on large Chinese populations, and is also consistent with reports from large Caucasian populations [10]. It is interesting that discrepancy exists among ethnic groups in the blood pressure differences between genders. Albeit the systolic pressure in both Asia and Caucasian are higher in males than females, African females were reported to have the same or even higher systolic pressure as compared to African males [3-10]. Based on Dr. Zhou's polymorphism frequency statement [16 17], the gender differences of blood pressure in Chinese population and the discrepancy of such difference among ethnic groups could be partially explained by the altered polymorphism frequencies through genetic drift.

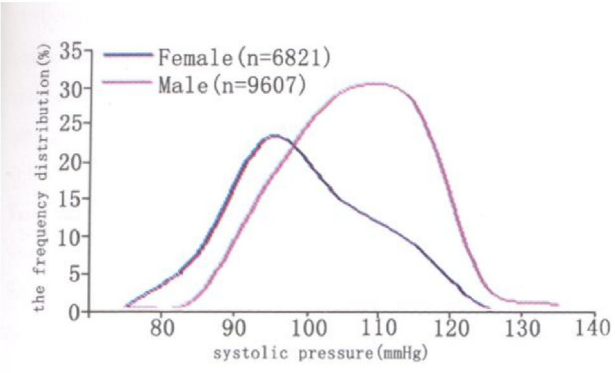

Figure 1. Different average systolic pressures between male and female undergraduates These blood pressure values were obtained using mercurial sphygmomanometer. A significant difference was seen in the major peaks between genders. Most females were between 100 to 110 mmHg and most males were between 110 to 120 mmHg in their systolic pressure.

2 Different hypertension complications between genders

The Chinese and Caucasian male adults have higher blood pressures as compared to female adults [9 10 12 13]. This fact has been under consideration empirically in the diagnosis of early stage hypertension and particularly in the timing of antihypertensive therapy regardless of an identical criterion of hypertension applied to both males and females. The slow progression and delayed organ damage of primary hypertension prevent us from better understanding the pathologies of early stage hypertension, particularly in young ages. For example, death rates from heart diseases in subpopulation between 15 and 35 years old are about the same in males and females of any ethnic groups.

End organ damages and relevant clinical incidents of hypertension have been well recognized and are the focus of hypertension therapy. However, death rates caused by many of the hypertension complications such as heart disease and cerebrovascular diseases are age, race, and living environment dependent, which may conceal the portion attributed to the factor of genders. Heart disease is the major complication of hypertension; however, it is difficult to reveal its gender difference when overall heart disease death rates are compared. As age and ethnics have strong effects on hypertension and its complications, it needs to be kept in mind that gender effect is only able to be revealed in carefully selected subpopulation. According to the 2007 USA statistic data (Figure 2), there is an ethnic group-dependent difference between genders in the death rates of heart diseases in subpopulations excluding those younger than 25 or older than 65 years of age. One emerged from this latest statistic data is the association of the gender differences of heart disease death rates among races with that of the aforementioned blood pressure differences.

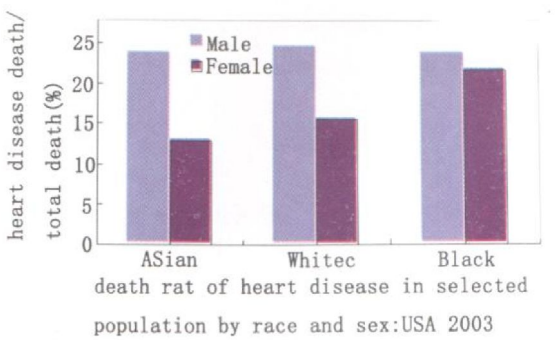

Figure 2. Gender and race differences of heart disease death rates These data were reformatted from 2007 National Vital Statistics Reports of USA.

3 Differences in response to pro-hypertensive and anti-hypertensive agents between genders

In addition to the influence on the timing of antihypertensive therapeutics, gender differences of blood pressure have substantial effects on drug responsiveness[18]. From the molecular point of view, it is the genetic polymorphisms of certain genes that form the gender differences of blood pressure among races, rather than the gender determining gene. Thus, a clinical dilemma is how to further classify patients into subgroups simply depending on their responsiveness to different types of drugs or drug combinations. Similarly, differences in response to pro-hypertensive agents between genders have been well observed, but the clinical implication has virtually ignored. For example, Khalid reported that gonadectomy abolishes the hypertensive response to salt overload, decreases gene expression and density of alpha-2B-adrenoceptors, and prevents their salt-induced up-regulation[19]. Whereas experimental data has clearly showed that maneuvers targeting androgen have significant effects on blood pressure, no such treatment has been employed or suggested in clinical practice yet[14,15]. Clinical trial using anti-androgen drugs should be a choice in the treatment of refractory hypertension or hypertension crisis, and this will make genetic polymorphism data available in the near future.

The renin-angiotensin system is the most important regulator for blood pressure homeostasis, and is believed to be far more complex enzymatic cascade than realized previously. Significant sex-specific differences in the regulation of the renin-angiotensin system and arterial pressure was observed in a study with rats[20]. While low-dose angiotensin II did not have an effect in males, it significantly decreased arterial pressure in females (14 mmHg). This decrease in arterial pressure in females was abolished by angiotensin II type 2 receptor (AT2R) blockade. When high-dose angiotensin II was infused, the hypertensive effect in females was significantly lower than that in males (48 mmHg versus 25 mmHg). This observation by Amanda et al might be a partial explanation for the different effectiveness of angiotensin converting enzyme inhibitors (ACEI) between male and female patients[21]. As show in Table 2, women showed less effect and more side effects after administration of ACEI. In addition to the rennin-angiotensin system, experiments with rats revealed sexual dimorphism in cafeteria diet-induced hypertension[22] and in NG-nitro-L-arginine methyl ester (L-NAME) induced hypertension[23]. Feeding male, female, and testosterone-treated female rats a cafeteria diet for 10 weeks increased body fat mass, plasma insulin, and leptin levels in all rats. Hypertension only developed in male and testosterone-treated female cafeteria-fed rats, and binding analysis revealed leptin receptor (Ob-R) protein down-regulation in hypertensive rats[22]. Although the gender difference with nitric oxide inhibition is not as dramatic as the one with cafeteria diet induced hypertension, still, male L-NAME-treated rats developed higher blood pressure (BP), popular rotorcraft association (PRA) and proteinuria than female rats. Interestingly, male rats were more resistant to the development of cardiac hypertrophy after the inhibition of nitric oxide production[23].

Table 2. Sex differences in response to pro- and anti-hypertensive reagents

Drugs	Male rats or men	Female rats or women
Angiotensin II (low dose)	Increase BP	Decrease BP
Angiotensin II (high dose)	More increase in BP	Less increase in BP
ACE inhibitors	More effective, less side-effect	Less effective, more side-effect
L-NAME	More increase in BP	Less increase in BP
Cafeteria diet	hypertensive	Not hypertensive
Aspirin	More effective in primary prevention of Myocardial infarction	More effective in primary prevention of stroke
Digitalis	Less reported deaths	More reported deaths
Beta-blockers	More effective	Less effective, more tachycardia

The parameters in italic obtained from experimental observation using rats

4 Impact on genetic dissection of hypertension

More than one thousand loci or genes associated with monogenic diseases have been either cloned or localized. However, it is more difficult to clone genes governing polygenic traits or diseases. This is partially due to the technical bottleneck, since the association analysis used in cloning genes of polygenic traits is less efficient as compared to the linkage analysis for monogenic trait dissection based on the law of segregation. The former rely on large number of individuals, while the latter only requires a small number of patients in one or a few families. One latest example of cloning genes governing polygenic traits is the determination of human high mobility group AT-hook 2 (HMGA2) gene after genotyping nearly 30 thousands individuals[24]. The genetic polymorphism of HMGA2 was reported to respond for approximately 0.4 cm increased adult height per C allele in 0.3% pop-

ulation. Clearly, the key factor between monogenic and polygenic genes is their penetrances. The more genes involved in the regulation of one trait it requires, the lower penetrance of each gene it possesses.

Blood pressure is a vital trait for life, which is regulated by the involvement of a number of genes. Accordingly, the cloning of genes governing the physiological range of blood pressure as well as the development of primary hypertension is labors, due to the technical difficulty in the determination of genotype-phenotype relationship. As discussed earlier, the gender differences in blood pressure in Asian subpopulation is the most significant among all ethnic groups. Our recent study showed that the gender differences of blood pressure are as nearly 10% of the normal level (Figure 1), which could be a precious genetic resource and may facilitate the identification of genes associated with blood pressure regulation as well as in the development of primary hypertension.

One mystery in regulating gender differences is genetic imprinting mechanism. It is possible that some imprinting genes play their effects on blood pressure regulation in a way dependent on the different hormones between genders, and some other imprinting genes may have their effects independent on sex hormones[25]. It was reported that maternal low protein diet (LPD, 9% casein vs 18% casein control) fed exclusively during the rat preimplantation period induced low birth weight, altered postnatal growth and hypertension in a gender-specific manner. A significant reduction in H19 (9.4%) and Igf2 (10.9%) mRNA was also observed in male, but not in female, fetal liver at day 20 postcoitum in response to maternal LPD restricted to the preimplantation period[26]. How these two imprinted genes regulate gender specific postnatal hypertension is still to be evaluated. As primary hypertension is a polygenic disease, it is a technical challenge in developing method to dissect the molecular basis of sexual difference, ethnic difference, and interaction of genes and gene-environmental factors. A recent bioinformatic study may pave a new avenue for the molecular dissection of genes involved in the sexual differences in hypertension. By analyzing Framingham Heart Study data, nine SNPs with imprinting effect were identified. Although the associations of five of these nine SNPs have been reported in human studies, Kwong et al have found the associations of four additional SNPs in humans, rs1979148, rs17476063, rs13076104, and rs9866277, which were only reported in rat before. Furthermore, there is no previous report of imprinting or maternal effect for any of the nine detected SNPs, whereas the model detected potential imprinting effects for three and maternal effects for five of the SNPs[26].

Whether genes or gene polymorphisms governing the gender differences of blood pressure are also associated with the development of hypertension complications is to be elucidated. Theoretically, the genes regulating these complex traits are superimposed: some polygenic loci associated with hypertension are related to the development of hypertension complications but some others may not be. Interestingly, a recently study reported some candidate genotypes associated with coronary heart disease in males of the United Kingdom[27]. It is possible that the complex traits other than reproductive system regulated by genes or gene polymorphisms with gender differences are much more than what we previously thought. Therefore, critical study about gender differences has enormous role in the cloning of genes associated with polygenic diseases, which will eventually facilitate the progress of individualized medicine.

5 Concluding remarks

Hypertension is one of the leading diseases in civilized societies. Genetic analysis of this and many other polygenic diseases is an urgent issue in biomedical research in the postgenomic era. This paper focused on the gender differences of blood pressure and suggested their enormous potentials in cloning genes related hypertension. Based on these discussions about molecular genetics of blood pressure and hypertension, we have learnt some general knowledge regarding to studies of the genotype-phenotype relationships. Firstly, significant phenotypic differences between subpopulations such as by gender or race are precious genetic resources in molecular dissection of polygenic traits or polygenic diseases. Secondly, not all abnormalities of polygenic traits are necessarily polygenic disease: some may consist of a mix of monogenic and polygenic diseases and some others may merely be a set of monogenic diseases. Finally, it is possible that some genes associated with polygenic traits are not highly mutable or not mutable at all. In other words, some genes are trait-level housekeepers. Current molecular dissection for genotype-phenotype employs linkage analysis for monogenic diseases and association analysis for polygenic diseases. New advances in biotechnologies including conditional gene knockout and siRNA silencing are expected to facilitate the pace in molecular genetics of polygenic diseases.

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血压的性别差异及其生物学意义

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[关键词] 性别; 血压; 高血压; 多基因病

[摘 要] **目的** 原发性高血压是世界上公认的多基因疾病。尽管人类基因组计划的完成大大加快了许多单基因疾病的基因的鉴定,但与原发性高血压相关基因的克隆仍然是生物医学研究面临的巨大挑战,其日益高涨的发病率及心血管并发症的高死亡率向人们提出了一个非常紧迫的问题,即怎样才能有效鉴定原发性高血压这个多基因疾病的相关基因。早在一百多年前,研究者就发现高血压有着明显的性别差异。并且,在许多少数民族人群中,男性与女性相比,不仅有着有着较高的平均生理血压值,而且还有着较高的高血压发病率。使男性有着较高生理血压值的基因或遗传多态性可能是高血压的易感因素,而激素相关基因或印迹基因则被认为参与了生理血压和高血压的性别差异的形成。此外,在临床实践中,血压的性别差异对促高血压药物或抗高血压药物的反应也有着显著的临床意义。因此,较好地了解血压的性别差异的分子遗传学可以有效地完成高血压形成相关基因鉴定,并最终促进高血压病的诊断和治疗的发展。本文主要揭示了血压的性别差异现象及其在基础血压研究和高血压相关的临床实践中的影响。

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