Research status of pulse pressure

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Abstract: Pulse pressure is the result of the periodicity of cardiac contraction and the nature of arterial circulation. Pulse pressure is affected by age, gender, height, heart rate, cholesterol, diabetes, hypertension, homocysteine, pulse pressure amplification, atherosclerosis, arteriosclerosis, coronary artery perfusion and other factors. As an independent risk factor for the occurrence of coronary artery stenosis, coronary heart disease, myocardial infarction and cerebral apoplexy, pulse pressure is even more valuable than systolic and diastolic blood pressure in predicting atherosclerosis, cardiovascular and cerebrovascular diseases and death. Previous studies have confirmed that pulse pressure is closely linked to genetic polymorphism of multiple genes. Some scholars have reported that pulse pressure is significantly correlated with the SNPs of angiotensin converting enzyme (ACE) gene, endothelial nitric oxide (eNOS) gene and dopamine receptor gene, etc. The change of pulse pressure is affected by multiple SNPs.

1. Introduction

Pulse pressure represents the difference between systolic and diastolic pressure, and the normal value is 30-40mmHg. The increasing of pulse pressure indicates poor artery elasticity. Pulse pressure is a mager phenotype of arterial elasticity, which is an independent risk factor for the disease of the heart. With the rapid progress of the genetics of heart and cerebral vascular disease and the study of arterial resilience, a growing number of cohort studies have confirmed that the pulse pressure is an isolated risk factor for coronary artery stenosis, coronary heart disease, myocardial infarction and stroke. Pulse pressure predicts atherosclerosis, cerebral vascular disease and death, even greater than systolic and diastolic pressure[1-4]. Therefore, as early as in 1999, the World Health Organization and the international hypertension federation proposed in the guidelines on the treatment of hypertension that pulse pressure and arterial elasticity parameters as independent indicators have important values in the study of the prognosis of hypertension[5].

2. The mechanism of pulse pressure

2.1. Model of pulse pressure

Pulse pressure is the result of periodic and cyclic properties of heart contraction. Therefore, although the average arterial pressure can be fully described in terms of output and total peripheral resistance, the source of pulse pressure is more complex. So no simple cycle model can explain the pulse pressure. The pulse pressure will be discussed from the comprehensive aspects of two complementary model systems, known as the windkessel model based on the characteristics of the circulation of the artery. The windkessel model is used in the simplest form of double components, describing the circulation with parallel resistance and capacitance components. The resistance component corresponds to the measured peripheral tube resistance, which corresponds to the circulation compliance of the artery. Compliance is a straightforward measurement capacity containing structure, in which case the arterial system is used to accommodate further volume (D volume/D pressure). Regardless of the fact that compliance is widely distributed in arterial trees, systemic arterial compliance is mainly determined by the aorta[6] and its main branches. Arterial compliance can be estimated by the attenuation of diastolic blood pressure[7] and a simpler method: compliance=stroke volume/pulsepressure estimation. Studies have demonstrated that there is a reasonable correspondence between these methods[8-9]. An important feature of the arterial system depends on the initial load conditions, which becomes smaller under higher pressure. This is not only important for the windkessel model, but also has an important impact on the transmission or propagation of subsequent discussions. Obviously, the high pulse pressure may be due to the increase in stroke volume or the decrease in compliance. With the increasing of the age of healthy subjects, pulse pressure or systolic pressure appears to be related to the decline in compliance. The increase in the pulse pressure of young people appears to be related to the increase in stroke volume.

The windkessel model is restricted in its analysis, because it classifies the arterial tree as the existence of compliance and resistance. Assume that all pressure changes occur instantaneously and the cycle allocates cardiac output through a series of branching networks. Hence, the windkessel model cannot

explain the phenomena with distributed systems, such as wave reflection and frequency dependence. This is especially significant for understanding pulse pressure. Wave reflection occurs in each branch of the arterial tree: a portion of the advancing pulse wave is reflected back to the heart, where it is combined with the advancing pulse wave. The frequency, distance and the dependent inhibition of the forward traveling wave and the backward traveling wave occurred. Therefore, the reflected waves returning to the heart mainly come from the terminal of the aorta and its major branches and gradually decrease[10]. This is due to the distance between these points and the heart, leading to decreased inhibition and reflexes.

The correspondence of forward and backward waves will also be determined by their corresponding time at any given measuring point. The increase of central systolic pressure refers to the superposition of positive travelling wave generated by visible reflection wave and left ventricle (LV) ejection. This change in the superposition of the aortic indentation is usually obvious. It may cause contractile pressure (and the resulting pulse pressure) to exceed the pressure generated by LV ejection alone. On the periphery, pulse pressure amplification refers to the amplification of the pulse pressure measured by the peripheral arteries relative to the proximal aorta. Although the magnification of the brachial artery is lower than that of the femoral artery, and it is also lower in the elderly than in the young, it is important to note that the peripheral estimates of pulse pressure are not the same as the measured central pulse pressure.

Therefore, pulse pressure depends on the characteristics of LV ejection and arterial wall, which determines the compliance and conduction characteristics of the arterial system. Although the dual windkessel model has the advantage of its simplicity, including the ability to describe the arterial system through simple numbers (i.e., compliance and resistance), it cannot describe other important determinants. Since both approaches are related to the same rationale, they may differ depending on the situation.

2.2. Factors affecting pulse pressure

2.2.1. Age, sex, height, heart rate

Aging is associated with the loss of elasticity of the aorta and major ducts. The increase in large artery, particularly aortic, stiffness resulting from fragmentation and disruption of elastin ratio is of profound importance to the genesis of increased pulse pressure with age[11-13]. The consequences of this increase in stiffness are important in both windkessel and propagative models of the circulation by leading to both reduced arterial compliance and

increased pulse wave velocity(PWV). Reduced compliance will increase pulse pressure because the buffering capacity available from the arterial wall is reduced, Increased pulse velocity will increase systolic blood pressure.

Loss of arterial elasticity, in the absence of compensatory dilation, both reduces arterial compliance and increases the velocity of wave propagation, which depends on the characteristics of the vessel wall given by bramwell-hill and moens-korteweg equations. The latter effect causes the reflected pressure wave to return early. Therefore, reflection waves are superimposed early in the systolic period, leading to an increase in systolic pressure, thus increasing central pulse pressure. The ratio of the forward traveling wave to the backward traveling wave and the position of the main reflection also change the amplitude and time of the reflection wave, thus increasing the central pressure. Animal data suggest that an increase in branching atherosclerosis with age may cause changes in these mechanisms, but there is no evidence to support this recommendation in humans[14]. The return time of the reflected pressure wave also depends on the distance to the main reflecting point and therefore on the height of the body. There is ample evidence for a relationship between increased central pressure and height[14-15]. This relationship may make a difference between men and women. In fact, women gain more weight than men[15]. Whether there is an independent difference in body size is less certain. The center coincidence of front and rear waves also depends on the time of ventricular ejection. Due to the proportional relationship between the ejection time and the duration of the cardiac cycle[16-17], when the heart rate is slow, the peak of the positive traveling wave will be relatively delayed. Therefore, even with a fixed reflection point and wave propagation velocity, the relationship between front and rear waves will change. The central pressure increases, so the central pulse pressure will be amplified at a lower heart rate[18]. As a result, the effect of being short is partly offset by a slightly faster heart rate in women.

2.2.2. Cholesterol, diabetes, hypertension, homocysteine

Some pathophysiological conditions have also been shown to influence the characteristics of the aorta. Interestingly, elevated cholesterol levels in the absence of significant atherosclerosis appeared to be associated with decreased aortic stiffness. In a study of asymptomatic patients with hypercholesterolemia, aortic stiffness increase less with age than in the control group[19]. Similarly, very young subjects with familial hypercholesterolemia shows more compliant aorta[20], while older subjects with

familial hypercholesterolemia shows decreasing arterial compliance in one study[21] and the opposite result in another[22]. The latter study finds any relationship between standard lipid variables and aortic compliance, but aortic compliance decrease with increase levels of oxidized LDL. Aortic stiffness is negatively associated with LDL cholesterol in asymptomatic 35-year-old men[23]. A similar pattern is seen in diabetes, where earlier studies have found increased arterial compliance in younger patients with type 1 diabetes and less arterial dilation in older patients with type 2 diabetes, who may have macrovascular disease[24]. People with diabetes seem to be particularly susceptible to reduced compliance from high-salt diets [25], but responses to fish oil in addition to diabetes, hypertension has been found to reduce brachial artery dilation [26]. Arterial compliance was lower in patients with salt-sensitive hypertension than in those with salt tolerance[27]. Although elevated plasma homocysteine is associated with systolic hypertension[28], it has little effects on the stiffness of the carotid or femoral arteries[29].

2.3. Pulse pressure amplification

Measurements of brachial arterial pressure are also affected by changes in the nature of the aorta. Arterial pressure is circumferentially transmitted with amplification of arterial pressure. Mechanisms propose to explain this phenomenon include distal reflection[30] and nonlinearity of positive traveling waves from the heart[31]. This leads to a difference in central-peripheral pulse pressure, which decreases with age due to the effect of hardening of the arteries as central systolic blood pressure increases. The relationship between brachial pulse pressure and height indicates that peripheral pressure amplification is also affected by transmission length[32]. Brachial systolic blood pressure and pulse pressure increased with age. Data from the United States shows that the increase in brachial pressure is greater in women than in men as they age, but this is not evident in all populations.

Pulse pressure amplification may have important consequences when considering clinical endpoint studies. Most of these studies measured brachial artery pressure, and important pathophysiological consequences of PP changes are associated with central pressure, such as cardiac hypertrophy and coronary perfusion. The difference between central and peripheral pulse pressure decreases in importance with age, but it is important not to ignore its potential effects.

2.4. Atherosclerosis and arteriosclerosis

It has been recognized that coronary atherosclerosis is often associated with other major

vascular diseases, particularly the thoracic and abdominal aorta[33], even at an early stage. In fact, one explanation for the association between elevated inflammatory risk markers such as c-reactive protein and future coronary events[34] is that such elevated levels are markers of a broad atherosclerotic process. The aorta and large aorta are known to harden with age, but some studies have found that this effect is amplified by widespread atherosclerosis. Therefore, measurement of the stiffness of proximal ascending aorta, aortic arch and abdominal aorta all shows increasing aortic stiffness in patients with coronary heart disease[34-35]. Similarly, in these patients, the arterial compliance value, which is mainly contained within the aorta, also decreased significantly [36]. There have also been negative studies, but these studies did not identify subjects based on clinical manifestations of coronary artery disease. In a study of asymptomatic men, estimated aortic compliance with pulse wave velocity was not associated with coronary calcification as determined by ultra-fast computed tomography. However, compliance with mean arterial pressure did correlate negatively with the number of extravascular lesions, but only before adjusting for age. As discussed, it has become increasingly clear in recent years that systolic and pulse pressure are more accurate predictors of coronary events than diastolic blood pressure. Both systolic and pulse pressure are the result of increased arteriosclerosis[37-38]. In a recent study, we were able to demonstrate that elevated pulse pressure in patients with coronary heart disease is closely related to increased aortic stiffness measured by echocardiography[39].

2.5. Coronary artery perfusion

Another phenomenon may limit the potential benefits of lower blood pressure which has to do with coronary artery perfusion dysfunction. Experimental studies have demonstrated that proximal cirrhosis or the using of cirrhotic bypass circulation is associated with decreased coronary artery perfusion. It is particularly evident in subendocardial and coronary artery stenosis[40]. This may be exacerbated a decrease in the mean stress by treatment. The potential adverse effects of blood pressure reduction have previously been demonstrated in humans to be associated with a J-shaped curve between blood pressure therapy and coronary outcomes[41-42]. In the recently published best treatment study for hypertension, cardiovascular mortality was increased in subjects with diastolic blood pressure down to 80 mmHg, and stroke mortality was further reduced.

In general, arteries (mainly aorta) harden, such as increasing pulse pressure by decreasing compliance and increasing pulse wave velocity as they age. As the systolic pressure increases, an increase in the

pulse wave velocity results in an early return of the reflected wave. Due to the nonlinear stress-strain behavior of the arterial wall, an increase in mean blood pressure also leads to an increase in pulse pressure, resulting in an increase in stiffness at higher inflation pressures. The coincidence of changes in the base wave height and heart rate, and the short stature, slow down the heart rate, leading to an increase in systolic blood pressure and pulse pressure. Comparing the pulse pressure between the population or study group requires consideration of these joint measurement factors, including the effects of pulse pressure amplification at the surrounding site. Some evidence suggests that atherosclerosis itself is associated with an increase in aortic stiffness (and a decrease in compliance values), not just because of age. Increased pulse pressure may aggravate myocardial ischemia because of increased afterload and reduced coronary perfusion.

3. Relationship between pulse pressure and cardiovascular and cerebrovascular diseases

The difference between systolic and diastolic blood pressure represents a component of blood flow pulsation, the value of which depends on the elasticity of the systolic jet dilatation catheter arteries and arterial vessels to accommodate large jets of blood and recovery of arterial volume. Therefore, pulse pressure is an indirect measure of arterial stiffness, which can lead to damage to the small blood vessels of the heart and brain, and is associated with severe cardiovascular and cerebral morbidity and mortality. Increased pulse pressure can significantly accelerate the process of arteriosclerosis. Pulse pressure and arteriosclerosis are mutually causal and form a vicious circle. Studies have shown that wide pulse pressure leads to greater traction of arterial vessels, acceleration of degeneration and fracture of elastic fibers, aggravation of coronary atherosclerosis, induction of atherosclerosis and thrombotic events, and remodeling of coronary arteries to reduce coronary blood flow reserve. The relatively high systolic blood pressure can directly increase the systolic ventricular load, promote ventricular hypertrophy, heart failure, and increase myocardial oxygen consumption; while the relative low diastolic blood pressure reduces coronary blood supply, which is more significant when there is cardiac hypertrophy. In addition, the change of shear stress at high pulse pressure can increase the tension of the plaque fiber cap, which causes the plaque to be easily broken and induce plaque instability. A large number of clinical trials and epidemiology have revealed that pulse pressure is an important independent risk factor for cardiovascular and cerebrovascular events. Pulse pressure increases, which increases the damage to cardiovascular and cerebrovascular diseases, which in turn leads to an increased incidence of cardiovascular and cerebrovascular events.

3.1. Pulse pressure and cardiovascular disease

3.1.1. Pulse pressure and coronary heart disease, arrhythmia

Pulse pressure is not only an important predictor of cardiovascular disease, but also an effective indicator of the extent of coronary artery disease, and more closely related to the incidence of complex arrhythmias. Tokitsu, et al.[43] showed that patients with high pulse pressure coronary heart disease (n=188) had higher rates of cardiovascular events than patients with low pulse pressure coronary heart disease (n=313), and pulse pressure was an independent predictor of coronary heart disease. Gaowa Ha Si[44] selected 90 patients with coronary heart disease as the study group, and selected 60 healthy subjects in the same period as the control group for pulse pressure level test. The results showed that there were significant differences in pulse pressure levels between patients with different lesion counts and coronary stenosis ($P<0.05$). Hanmin Gu, et al. [45] showed that the incidence of complicated arrhythmias in hypertensive patients with pulse pressure ≥ 50mmHg was significantly higher than that in patients with pulse pressure<50mmHg. Jie Xie, et al.[46] divided 154 cases of coronary heart disease with hypertension according to 24h mean pulse pressure into two groups A (pulse pressure<50mmHg) and B (pulse pressure ≥ 50mmHg), comparing the degree of coronary artery disease and arrhythmia. The incidence of 3 lesions and the number of lesions in group B were significantly higher than those in group A ($P<0.01$), and the incidence of complicated arrhythmia was significantly higher than that in group A. From the above studies, it is known that the increase in pulse pressure indicates an increase in the incidence of coronary heart disease and complex arrhythmia.

3.1.2. Pulse pressure and cardiac hypertrophy, heart failure

Hypertension is one of the main causes of cardiac hypertrophy. Increased pulse pressure in hypertensive patients is closely related to the occurrence of left ventricular hypertrophy, and heart failure can eventually occur. Xiuzhen Yu, et al.[47] divided 191 elderly patients with hypertension diagnosed in hospital according to 24 hours of the average pulse pressure (APP) into low pulse pressure group (24h APP<60 mmHg, n=136) and high pulse pressure group (24h APP ≥ 60 mmHg, n=55), the left

ventricular mass index was calculated. The simple linear regression showed that the 24h APP and 24h dynamic pulse pressure index were risk factors for left ventricular hypertrophy. Multivariate stepwise linear regression can be used to analyze 24h dynamic pulse pressure. The index is an independent risk factor for left ventricular hypertrophy. Hongqi Sun[48] showed that the pulse pressure is greater in the study of pulse pressure and cardiac hypertrophy, the higher the incidence of left ventricular hypertrophy. Zepeng Lin et al.[49] divided 336 elderly hypertensive patients into four groups of ≤48, 49-58, 59-68, and >68 mmHg according to pulse pressure level. Logistic regression result shows pulse pressure and cardiac function and vascular endothelial growth factor (VEGF) and high sensitization C reactive protein (hs-CRP) in each group. The results showed that with the increase of pulse pressure, serum VEGF and hs-CRP levels were significantly increased (P<0.01), left ventricular systolic and diastolic function were significantly decreased (P<0.01, P<0.05). This proves that there is a significant correlation between pulse pressure and left ventricular dysfunction in elderly hypertensive patients. Wenchu Liang, et al.[50] divided 62 patients with organic heart disease into heart failure and non-heart failure group, and measured the 24h mean pulse pressure difference of the two groups and compared them. The results showed that the 24h mean pulse pressure difference in the heart failure group was higher than that in the control group (P<0.01). It can be seen that the increase in pulse pressure is closely related to cardiac hypertrophy and heart failure.

3.2. Pulse pressure and aortic disease

Studies have shown that increased pulse pressure is closely related to changes in aortic elasticity and compliance, and it is an important indicator of arteriosclerosis. Wang Haiyan, et al.[51] selected 68 patients with hypertension to record 24h APP and carotid intima-media thickness to determine carotid atherosclerosis. Logistic regression analysis showed that the higher the APP in hypertensive patients, the higher the incidence of carotid atherosclerosis, APP is risk factors for carotid atherosclerosis. Yuxin Song[52] selected 45 elderly patients with simple systolic hypertension in our hospital over a two-year period and compared them with those with normal pulse pressure. It was found that pulse pressure was positively correlated with carotid artery intimal thickness, with increased pulse pressure and carotid artery intimal thickness. Pulse pressure maybe an important risk factor for atherosclerosis in elderly patients with simple systolic hypertension. Cheng Jiang[53] also got similar conclusions. It can be seen that pulse pressure is an important risk factor for carotid atherosclerosis.

3.3. Pulse pressure and cerebrovascular disease

In recent years, a large number of studies have also proved that pulse pressure is an important risk factor for stroke in middle-aged and elderly people. OkadaK[54] confirmed that pulse pressure was not only related to stroke but also increases with pulse pressure in middle-aged people. The prevalence rate has also increased. Xiang Chunxia, et al.[55] selected 1881 patients with ischemic stroke and used Logistics regression to analyze the risk of hospitalization death at different pulse pressure levels. It is concluded that pulse pressure is a risk factor for death during hospitalization for ischemic stroke, and the risk of death from pulse pressure ≥70 mmHg is greater. Linna Zu, et al.[56] showed that the pulse pressure level was positively correlated with the prevalence of ischemic stroke, and the prevalence rate gradually increased with the increase of pulse pressure.

4. Genetic polymorphism

Single nucleotide polymorphism mainly refers to the DNA sequence polymorphism caused by the variation of single nucleotide at the level of genome[57]. As a new genetic marker, SNPs has been widely used in the genetic anatomy of complex traits and diseases and the research of population-based gene recognition. Previous studies have confirmed that pulse pressure is closely related to genetic polymorphism of multiple genes. Some scholars reported that pulse pressure was significantly associated with the SNPs of angiotensin converting enzyme (ACE) gene, endothelial nitric oxide (eNOS) gene and dopamine receptor gene. In 2011, Verwoert GC, et al. found four new pulse pressure sites by studying the GWAS(Genome Wide Association Study) of 74064 baseline patients and 48,607 follow-up patients. All P values were between P=2.7 10-8 and P=2.3 10-13[58]. In 2012, a twin sample of homozygous twins over the age of 35 was selected in the twin study in China. Affymetrix Genechip Genome-Wide Human SNP Array 6.0 chip was used for genome-wide linkage mapping, which was found to be significant with pulse pressure. Sex-linked regions (Lod=3.6) are located on chromosomes 11, 12, and 18, respectively. The latter two peaks overlap the results of the two American populations. In addition, a number of linkage peaks with Lod scores greater than 3, suggesting that there may be potential linkages with pulse pressure, located on chromosomes 1, 3, 4, 6 (Lod=3.19), 7, 9, 17 and 22. On the basis of linkage analysis, a genome-wide association analysis indicates multiple gene SNPs sites with pulse-pressure-wide genome-wide association significancently (rs12067906, rs17031508, rs4580657, rs1223397, rs7984522).

These results are consistent with the chromosome linkage analysis, in which the rs1223397 (P= 1.04e-07) site locates in the PHACTR1 gene of the chromosome[59]. In 2013, Tanika NK, et al. performed GWAS meta-analysis on 28,783 east Asian population and verified two susceptibility loci related to pulse pressure -- rs17249754 of ATP2B1 gene (P=1.2 10-5) and rs11191593 of NT5C2 gene (P=1.1 10-3)[60]. Hypertensive patients and normal subjects, suggesting that carrying the adducinα subunit gene TT type, aldosterone synthase gene TC/CC type and ACE gene type DD are more likely to increase pulse pressure compared with other genotype, and it is an independent risk factor for increased pulse pressure[61]. In the study, Yonghong Niu also found that the β2-AR Arg16Gly gene polymorphism was significantly correlated with pulse pressure, and the β2-AR Arg16Gly gene polymorphism was also associated with aortic stiffness[62]. In 2015, based on a cohort study of metabolic syndrome in Jiangsu population, it was found that the A allele carrier of rs1805192 of PPARγ was associated with pulse pressure levels[63]. Analysis of the above research status shows that the change of pulse pressure is affected by a variety of gene SNPs, and the SNPs of related genes in the pathways of inflammation, cell proliferation and vascular remodeling may play an important role in the occurrence and development of abnormal pulse pressure.

5. Conclusion

Pulse pressure is affected by age, gender, height, heart rate, cholesterol, diabetes, hypertension, homocysteine, pulse pressure amplification, atherosclerosis, arteriosclerosis, coronary artery perfusion and other factors. Next, we should pay more attention to the influence of genes on pulse pressure. Pulse pressure is influenced by both environment and genes. By studying these two ways, we can find out more effective ways to control pulse pressure.

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