Blood Pressure Profile Along the Arterial Tree and Genetics of Hypertension

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The conformation of blood pressure curve varies extremely from larger to smaller arteries due to different predominant structure and functional properties of the arterial wall along the arterial system. The simple determination of two points of the blood pressure curve, systolic and diastolic blood pressure, has been used in most of epidemiologic and genetic studies on hypertension, without taken into account the difference profile of blood pressure curve along the arterial tree. Recently, non-invasive pulse wave analysis has identified measurements of arterial stiffness as an independent factor of cardiovascular risk in hypertensives. Different determinants of arterial stiffness seem to be genetically determined. Future studies on the genetics of hypertension should consider the blood pressure profile and its main determinants.

INTRODUCTION

High blood pressure is a major risk factor for cardiovascular complications as coronary heart disease and stroke. Risk relations for both systolic (SBP) and diastolic (DBP) blood pressure are generally regarded as continuous, graded, strong and independent of other risk factors. However measurements of both SBP and DBP are related to the steady component of blood pressure curve profile. The pulsatile component of blood pressure curve is dependent on arterial stiffness of large arteries and on wave reflections[1]. These components have not been taken into account in the epidemiologic studies regarding cardiovascular risk in hypertensive patients.

More recently, several epidemiological studies reported that pulse pressure (PP), the difference between SBP and DBP, is a useful predictor for coronary artery disease or total cardiovascular disease, especially in middle-aged or older persons[2-5]. Pulse pressure arises as a consequence of the episodic nature of cardiac contraction and the structure and function of the arterial circulation (Fig. 1)[6]. Thus, while cardiac output and total peripheral resistance adequately describe mean arterial pressure, the origins of PP are more complex. Intrinsically, PP is not explicable by any single, simple model of the circulation. It depends on left ventricle ejection and the properties of the arterial

wall, which determine both the distensibility and the transmission characteristics of the arterial system[6]. Loss of arterial elasticity, in the absence of compensatory dilation, will both increrase arterial stiffness and the speed of wave transmission due to the dependence of the latter on vessel wall properties. The latter effect will lead to earlier return of the reflected pressure wave. Hence, the reflected wave superposes earlier during systole, resulting in increased systolic pressure augmentation, thereby also increasing central PP. These characteristics are typically present in elderly persons with isolated systolic hypertension where the arterial stiffness is increased by fissuring and fracturing of the elastin protein, collagen proliferation, and calcium deposition, frequently associated with a widened and torturous aorta[7].
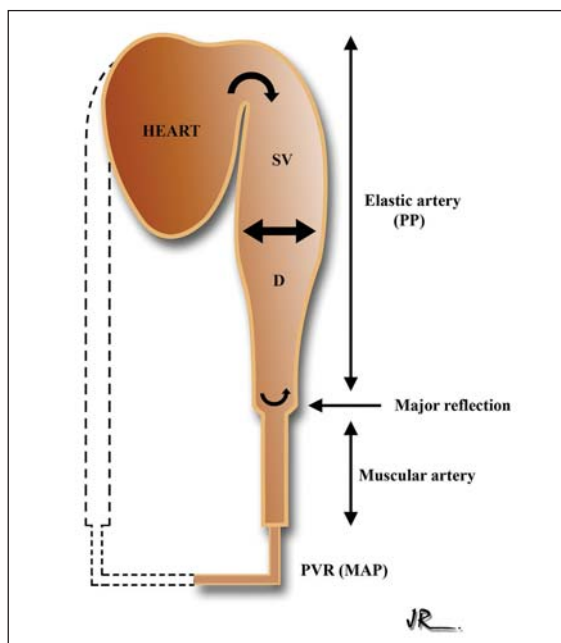

Fig. 1 – *Pulse pressure (PP) arises from the interaction between stroke volume (SV) and the characteristics of the arterial circulation that determine distensibility (D) and wave reflection. Cardiac output and peripheral vascular resistance (PVR) determine mean arterial pressure (MAP)[6]*

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These determinants of increased arterial stiffness and increased PP seems to be influenced by genetic factors independent of other classical cardiovascular risk factors[8,9]. The most important influence seems to be on the structural and functional properties of the large arteries. It has been previously demonstrated that genetic factors directly influence the structure of the arterial wall or act indirectly through age, blood pressure, smoking, cholesterol levels, and glycemia, finally resulting in an increase in arterial stiffness[9-11]. In this review we discuss the main physiological mechanisms that are involved in the blood pressure configuration along the arterial tree. Thus, we characterize the mechanical properties of large and small arteries and the main determinants of systolic, diastolic and pulse pressure in different arterial sites. These considerations have to be taken into account for future investigation on genetics of hypertension.

THE BLOOD PRESSURE CURVE ALONG THE ARTERIAL TREE

The aorta takes origin from the left ventricle and almost immediately curves, in a complicated three-dimensional way, giving off branches to the heart, head, and upper and lower limbs[1,12,13]. In general the size of individual branches corresponds well to the amount of flow they conduct, even if there are considerable variations. There is no doubt that, beyond the early branches, the total cross-sectional area of the arterial tree begins to expand dramatically. Whereas total cross-sectional increases, the average diameter is reduced, reflecting the increased number of bifurcations toward arterioles [1,12,13].

When along the arterial and the arteriolar tree, the forces governing flow are considered, they are exclusively interested in the pressure generated by the heart. This quantity is the difference between the actual pressure and its hydrostatic component, and is commonly referred to as "blood pressure" (BP). It is the gradient of excess pressure, which drives the flow. The distribution of excess pressure through the circulation, which is illustrated in Figure 2, is largely dissipated in forcing the blood through the microcirculation. Nevertheless, the cardiac pump is intermittent.
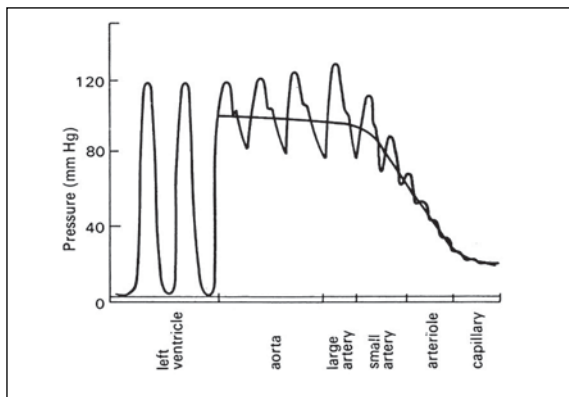

Fig. 2 – Intra-arterial blood pressure inside the left ventricular and the arterial and arteriolar circuit[2]. See text

Pressure rises rapidly in the left ventricle at the beginning of the systole, and soon exceeds that in aorta. Thus the aortic valve opens, blood is ejected, and aortic pressure rises. During the early part of the ejection phase, ventricular pressure exceeds aortic pressure. About half way through ejection, the two pressure traces cross, and there is now an adverse pressure gradient across the aortic valve, which is maintained as both pressures start to fall (dichrotic notch)[13]. At this point the pressure in the aorta falls much more slowly than in the ventricle because the large central arteries, and particularly the aorta, are elastic, and thus act as a reservoir during systole, storing some of the ejected blood, which is then forced out into the peripheral vessels during diastole (Windkessel effect) [1,12,13]. Now, if BP is examined at two points on the axis of aorta, it can be seen that the pressure records are almost identical in shape at the two sites, but the one at the downstream point is slightly delayed (Fig. 3). In other words, the pressure pulse generated by ventricular contraction is traveling along the aorta as a wave. It is possible to calculate its velocity (which is pulse wave velocity, PWV) from the delay if the distance between measuring sites is known (Fig. 3).
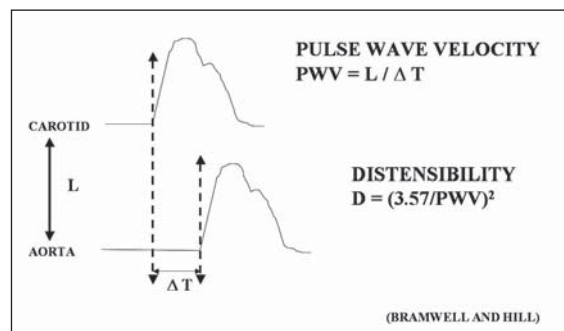

PULSE WAVE VELOCITY
$$PWV = L / \Delta T$$

DISTENSIBILITY
$$D = (3.57/PWV)^2$$

(BRAMWELL AND HILL)

Fig. 3 – Pulse wave velocity (PWV) measurement between the carotid and the femoral artery. PWV is the ratio between the 2 arteries, according to the Bramwell and Hill formula

If simultaneous measurements are done at several points all along the aorta, the pressure wave changes shape as it travels down the aorta. It is progressively delayed, but also steeping and increases in amplitude, whilst at the same time losing the sharp dichrotic notch (Fig. 2). Thus the paradox is that the systolic blood pressure (SBP) actually increases with distance from the heart. In fact, of course the mean level of the arterial pressure (MAP) falls with distance from the heart (the fall is only about 4 mmHg) along the length of the aorta, whilst the amplitude of the pressure oscillation between systole and diastole, which is pulse pressure (PP) nearly doubles. This process of PP amplification continues in the branches of the aorta out to the level of about the third generation of branches. Thereafter both PP and MAP decrease rapidly to the levels found in the microcirculation where a quasi steady flow is observed (Fig. 2). Whereas the macrocirculation is influenced by the concepts of propagation of pressure wave (Fig. 2 and 3), PWV and PP amplification, the microcirculation is influenced by

steady flow, as results from the Poiseuille's law[12]. The pressure gradient is then proportional to the velocity and viscosity of blood, to the length of the arteriolar tree, and mostly inversely proportional to the power four of vascular diameter.

Several animal studies have examined the hydrostatic pressure profile along the vascular elements between the heart and capillaries. The general consensus is that the BP decrease occurs predominantly in precapillary vessels ranging from 10 to 300 μm (Fig. 2). Conversely, a very high vascular resistance (which represents the mechanical forces opposed to blood flow) builds up abruptly from larger to smaller arteries, over a transitional short length of the path between arteries and veins, causing a dramatic decrease in MAP. The high resistance thus reduces both pulsatile phenomena and steady flow. At the same time, the PP amplitude decreases, resulting in almost completely steady flow through resistance vessels. A further contribution to opposition to flow derives from the reflection of arterial pulsations that cannot enter the high resistance vessels and are summated with pressure waves approaching the area of high resistance. This area of reflection is directly related to the number and the geometrical properties of the arteriolar bifurcations.

APPLICATIONS TO THE GENETIC ASPECTS OF CLINICAL HYPERTENSION

In traditional reports on genetics of human hypertension, the hypothesis that genetic variability could lead to high BP has been mainly tested on the basis of comparison of mean values of brachial DBP in parents with different genotypes[9,14]. In these studies, the classification of hypertensive subjects was constantly based on a single point of the cyclic BP curve, namely brachial DBP. The results were relatively limited since they excluded brachial SBP and PP, the major predictors of cardiovascular (CV) risk[1]. Furthermore, in humans, central BP, which differs markedly from brachial or radial BP, has never been systematically investigated in the past. As we have shown earlier, the aortic BP curve is the consequence of an interaction between two different components: a steady component, corresponding to MAP, and a pulsatile component, corresponding to PP. Whereas MAP, which is influenced by cardiac output and vascular resistance, refers to small arteries, PP refers to large arteries and is determined by ventricular ejection, the stiffness of large arteries, and finally the amplitude and timing of wave reflections[1,12,13] (Fig. 1).

Studies of knock-out mice have indicated that the two components of the aortic BP curve may be analyzed separately[15]. Genome-wide linkage analysis of PP have shown the importance of identifying genetic factors in subjects with high[16,17]. Evaluation of the totality of the BP curve, mainly of the aortic BP curve, is necessary for estimation of genetics of hypertension and arterial stiffness, since changes in one of the components may lead to different phenotypes of the BP curve. For instance, from the gene polymorphisms related to the renin-angiotensin system, those related to angiotensinogen rather reflect MAP whereas those related to angiotensin II-AT1 receptors or to angiotensin converting enzyme (ACE D/I) reflect rather PP and arterial stiffness[9,18].

One of the most important finding in subjects with hypertension results from recent studies on the ACE I/D gene polymorphism. Staessen et al[18,19] were the first to show that the DD genotype was significantly associated with hypertension, but mostly with isolated systolic hypertension in the elderly. In this population, the DD genotype was associated with increased arterial stiffness, a result observed both in diabetic and non-diabetic subjects, particularly above 50 years of age[10,11]. In old hypertensive subjects, those with DD genotype have an accelerated increase of PP with age, as a consequence of an accelerated lowering of DBP with age, and not of an accelerated increase of SBP with age[10,11]. Furthermore, in old subjects with systolic hypertension, recent research suggests that the combination of 2 or 3 specific gene polymorphism (ACE, aldosterone synthase and alpha-adducin gene polymorphisms) affect vessel wall mechanical properties more profoundly than a simple gene polymorphism[9,18,19]. Also, other polymorphisms have been associated to increased arterial stiffness and vascular hypertrophy, as those related to elastin and G protein genes[20,21].

CLINICAL IMPLICATIONS AND PERSPECTIVES

The present considerations indicate that the phenotypes of BP curve vary greatly from larger to smaller arteries and that age may greatly accentuate the differences between such phenotypes. This simple observation clearly shows that the traditional genetic descriptions obtained in hypertensive humans from two points of the BP curve, SBP and DBP, are oversimplified.

Further evidences for these finding result from non-invasive pulse wave analysis which has recently highlighted the role of PWV and wave reflections as independent factors of CV risk in subjects with hypertension[22-25]. Age influences greatly all these modifications and tends to increase PP more rapidly in the central than in the distal compartment of the arterial tree, resulting in an age-dependent reduction of PP amplification. This age-dependent reduction has been shown also to be an independent predictor of CV mortality in hypertensive subjects[26].

In summary, this description has shown that, in the CV system, elastic arteries buffer the pulsations,

muscular arteries actively alter propagation velocity and arterioles serve as major reflection sites to amplify BP changes. Any disturbance of such alterations may cause a predominant or selective increase of SBP and PP as observed in aged and/or hypertensive populations with high CV risk. Consequences of this knowledge on the genetics of hypertension should have to be taken into consideration in the future.

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