PRACTICAL SIGNIFICANCE OF INDIVIDUAL BLOOD PRESSURE TRAJECTORIES

T. Yaneva-Sirakova, Ivan Gruev¹, Arman Postadzhyan²
¹National Transport Hospital “Tzar Boris III” – Sofia, Bulgaria
²University Multiprofile Hospital for Active Treatment “Sveta Anna” – Sofia, Bulgaria

Abstract.
Individual blood pressure values tend to be close to a certain population pattern (because of environmental and socio-economic factors), without fully following it (because of specific individual genetic predisposition). These population “patterns” or ‘trajectories’ can be followed back to prenatal period and across the whole lifespan. Some of them are correlated with higher risk for development of arterial hypertension. There are also several “cornerstones” in these patterns, where the individual may be at an increased risk for movement to a higher-risk group. They can explain why certain individuals are more prone to target organ damage than others and why we, as clinicians, should have an individualized approach when we translate population-based guidelines to the single patient. Proper definition and practical knowledge of the significance of these blood pressure trajectories could be important for everyday prophylaxis and practice.

Key words: blood pressure trajectories/population, childhood, prenatal, target organ damage

Address for correspondence:
Teodora Yaneva-Sirakova, e-mail: teodora.yaneva@gmail.com

Резюме.
Индивидуалните стойности на артериалното налягане се доближават до определен популяционен модел (поради екологични и социално-икономически фактори), без да го следват напълно (поради специфична индивидуална генетична предрасположеност). Тези популяционни „модели“ или „траектории“ могат да бъдат проследени до пренаталния период и през целия живот на индивида. Някои от тях са свързани с по-висок риск от развитие на артериална хипертония. Има и няколко ключови (високорискови) моменти в тези модели, при които индивида може да бъде застржен от преминаване към група с по-висок сърдечно-съдов риск. Тези траектории на артериалното налягане и високорискови преходни моменти могат да обяснят защо някои хора са по-склонни към увреждане на целевите органи от други. Клиницистите трябва да подхождат индивидуализирано при приложението на насоките на база популяционните модели върху конкретен пациент. Правилното дефиниране и практическото познаване на значението на тези траектории на артериалното налягане може да бъде важно за ежедневната профилактика и практика.

Ключови думи: траектории на кръвното налягане/популация, детство, пренатално, увреждане на целевите органи

Адрес за кореспонденция: д-р Теодора Янева-Сиракова, e-mail: teodora.yaneva@gmail.com

INTRODUCTION

According to the current concepts there are three main groups of pathogenetic factors, that play the leading role for the development of essential hypertension [1]: 1) genetic predisposition [2], 2) environmental factors [3], and 3) aging [4, 5]. Neither of these groups of factors is self-sufficient to cause arterial hypertension and ultimately – target organ damage. Their interacci

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consider two major points of view when facing the “hypertension problem”: 1) Population, and 2) Individual. The environmental factors in terms of salt consumption, air pollution, exercise habits, chemicals, food exposure, etc. lead to a significant change (rise) in blood pressure, beginning from the earliest age, even prenatally [8, 9]. From the above, naturally follows that the different populations may have different predisposition to arterial hypertension. If the genetic predisposition is taken into consideration, there might be different population-based blood pressure trajectories. Individual values may be close to a given trajectory that is one of several possible for the given population. The practical significance of this issue is that the individual treatment – time and threshold values of initiation, continuation, target values, may vary according to this trajectory and not only according to the specific blood pressure values. Knowing the problem may help the clinicians in their decision-making when to screen and when to intervene, in order to achieve timely control of arterial hypertension.

**MAIN DOCUMENT**

**Evidence for blood pressure trajectories across lifespan**

The understanding that blood pressure (BP) rises with the advancing age was objected in several trials and the environmental factors were considered in the pathogenesis of arterial hypertension [10, 11].

Current concept postulates that aging is not enough to cause arterial hypertension and socioeconomic and environmental factors play a significant role [12-15]. A study of Liu et al followed 30 384 Chinese adults for 4 years and distinguished five BP phenotypic variants and assessed their relation to brachial-ankle pulse wave velocity (PWV): low-stable, moderate-stable, elevated-stable, elevated-increasing, elevated-decreasing [16]. There was a correlation between BP life trajectories and both initial and consecutive PWV. However, the study was of limited duration to lead to a definite conclusion for the adult lifespan.

In a study of Zhang et al, there were 5 systolic blood pressure (SBP) trajectories and 4 diastolic blood pressure (DBP) among normotensive young adults [17]. They tried to find the modifiable predicting factors for the development of hypertension among Asian population. Physical activity and low salt intake were found to be protective for the development of arterial hypertension. Such studies are a need in other parts of the world as the environmental factors may differ in the context of different socio-economic factors.

Several studies point out the origin of these BP trajectories from childhood or even prenatally [18]. They stem from factors such as: body mass index, skinfold thickness, waist circumference from ages 3 to 8, abdominal adipose tissue at 4.5 years, triglyceride levels. Insulin resistance at the age of 6, maternal BP during pregnancy and infant weight gain in the first 2 years of life. However, there is not a single study which encompasses the whole period – from the prenatal to the advanced age with the transitions of BP at times of excessive growth and hormonal changes.

As a conclusion: the current studies offer different points of view on a single problem – the significance of BP trajectories, with neither a clear definition, nor proper delineation of risk factors and the clinical significance of these trajectories.

**Critical periods in the lifespan**

There are three critical BP life-time periods which may become a turning point for the development of arterial hypertension and transition between the BP trajectories: adolescence; peripartum; advanced age/menopause [19]. Shen et al. showed that the puberty period was very important for the development of advanced-life hypertension [20]. Four major trajectories were defined from this point of development towards midlife: low-stable; elevated-stable; moderate-increasing; elevated-increasing. The finding was true for both genders and for various races. However, the pre-puberty BP values were negatively correlated with the adult hypertensive pattern – with a steeper slope of rise of BP. Thus, the hypothesis of hypertension as a “growth-related” disorder was introduced, with the explanation for a “regression to the mean” on population level [21].

The second critical period – the peripartal one, a female-specific period, may have a significant implication for the following – life BP values in two totally different directions: a stable rise or a stable fall in blood pressure, being a continuation of the rise (pathological) or fall of blood pressure during the peripartal period [19, 22]. The explanation of the first phenomenon is the continual rise of blood pressure in sensitive women and the understanding that this life-period unmasks an underlying problem, which might be just a matter of time to be clinically manifested. This thesis is proven in a meta-analysis of BP data from four community-based trials ARIC, [23]. CARDIA, [24]. MESA, [25]. FHS [26]. in which blood pressure rise in women is steeper than in men and the major rise comes in the third and fourth decade [27]. This is proven also in preeclampsia studies – once hypertensive during pregnancy – always hypertensive [28]. The second phenomenon was seen in the HUNT Study [29]. It comprises 125 000 Norwegian people with three population – based surveys (HUNT1, 2 and 3) and a significant relatively open access biobank, the results of the more than 20 years of follow
up showed that hormonally (progesterone) mediated decline of BP during pregnancy is perpetuated and postpartum with the net effect that parous women had lower BP values [30].

The third risk period for the clinical manifestation of hypertension is older adulthood. The pathogenesis of this process is well known and lies within the combination of the progression of atherosclerosis and arterial stiffness (or vice-versa) and the environmental factors – salt intake, sedentary lifestyle, obesity, glycemic control, that accelerate normal aging [31]. It should be noted that in later life BP values and arterial stiffness may go in opposite directions – with the rise of arterial stiffness BP falls because of frailty or autonomic dysfunction. The sex difference in BP during this period is nonsignificant [27]. However, women start at a relatively lower values and the consecutive postmenopausal rise should be interpreted as a steeper rise in BP than in men [32]. The maximal BP sex difference was observed around 26 years of age with the difference explained with various hormonal and epigenetic factors [33].

Several large cohort and prospective trials show that BP decreases 14-18 years before the end of life, due to dementia, heart failure, frailty, or simply as harbinger of the natural end of life [34].

**Blood pressure trajectories and target-organ damage**

Some of the BP trajectories can easily transform into overt hypertension. But if we consider the significance of the central aortic pressure – a clear delineation between certain borderline profiles and hypertension is clinically difficult [35]. Thus, we can confer that some of the BP trajectories may be associated with a significant unrecognized risk for target organ damage above the age-related one.

Liu et al, followed 4625 adults for the life-span period between 18-60 years. [36]. They recognized four BP trajectories: normotensive-stable, prehypertension-stable, stage I hypertension-increasing, stage II hypertension – increasing. The last two groups were associated with elevated risk of developing diabetes mellitus. The common pathway discussed was endothelial dysfunction [37]. And oxidative stress, resultant from arterial hypertension and impaired beta-cells [38, 39].

A 23-year follow-up of children to early adulthood with around 16 measurements showed that among the 683 participants, three major BP trajectories were found (low-increasing, moderate-increasing, high-increasing), which were independently associated with target organ damage – increased intima-media thickness and left ventricular mass index [40]. A Korean epidemiological study proved that elevated mid-life BP trajectories provoked cardiac atrial size changes [41]. Similar were the results from the Cardia Study, which proved an association between the BP trajectories of the highest profile in young ages and consecutive coronary artery calcification [42].

A follow-up of 30 years was conducted as part of the CARDIA study and the patients were divided in five distinct types of global BP tendencies: low-stable; moderate-stable; high-stable; moderate – increasing and high-increasing [43]. The last two – with continually rising mean values of SBP, DBP and PP, were associated with the most prominent myocardial remodeling in terms of impaired systolic and diastolic function in later life.

BP patterns in normotensives may predict the development of renal disease in later life [44]. Among 2430 people with moderate-stable, high-stable and moderate increasing groups 228 developed subclinical kidney injury for a follow-up of 30 years.

As a result, it naturally raises the problem of finding the different BP trajectories in populations of different cardio-vascular risk. Some studies define four, others – five or three types. Thus, we need a standardization to make better predictions and primary prevention especially in a high-risk population as the Bulgarian one [45].

**Gaps in evidence and further studies**

There is no proper and unified definition of what BP trajectory is, rather – an intuitive understanding of the problem is used. In different papers a different word is used to mark this blood pressure curve over the lifespan. We have chosen “trajectory”, and not “profile” or “pattern”, to stress on the fact that we have a process of progression and not a static depiction. However, BP “trajectory” is quite different from “overt” hypertension, and there should be a clarification when we diagnose “hypertensive” patients in the lowest BP trajectories, when to intervene to reduce the cardio-vascular burden. For this purpose, we must have a better knowledge of birth and childhood status. There might also be population differences in the threshold values, explained by the different ethnic and environmental factors. However, there are several patterns of time-changes in BP across life which are discussed in literature, such as the gradual rise in early life and the gradual fall near the end of life. Here we should mention another problem, that has been recently discussed in literature – the variability of a certain factor and whether we can consider these “BP variations over lifetime” an example of the pathological variability [46]. Future efforts should be made to clearly define these patterns, with variables’ thresholds in accordance with the specific local epigenic factors.
CONCLUSION

Based on the above trials and conceptions there are several major problems to be discussed: 1. the need for timely and continuous follow-up of people in the risky transitional lifetime points – from childhood into early adulthood, and then with advancing age to the most elderly people; 2. the timely start of treatment in high-risk groups; 3. the timely reduction of treatment in frail groups at advanced age; 4. the definition of specific population BP trajectories; 5. conduction of target- ed treatment initiation trials according to the specific BP risk profiles.

No conflict of interest was declared.

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