Early vascular phenotypes in the genesis of hypertension

Empar Lurbe · Maria Isabel Torró

Abstract Cardiovascular complications occurring in adults find their roots in risk factors operating early in life. Among the factors influencing cardiovascular risk, blood pressure values in children represent an important measurable marker of the level of potential cardiovascular risk later in life because the levels are both the cause and the consequence of early vascular alterations. Early vascular phenotypes represent a field of great interest, and they can be studied through indirect assessment using non-invasive techniques. Estimations of blood pressure components, pulse wave velocity, and reflecting waves provide valuable information that can be easily recorded and repeated over time. A direct assessment, carried out by examining the umbilical vessels, can add further valuable information. In this review, we discuss the potential application of surrogate markers of early vascular alterations and describe the information provided by umbilical cord vessels.

Keywords Blood pressure · Children and adolescents · Pulse wave morphology · Pulse wave velocity · Umbilical cord vessels · Vascular phenotypes

Introduction

Cardiovascular complications that occur in adults find their roots in risk factors operating early in life. Among the factors influencing cardiovascular risk, blood pressure (BP) values in children represent an important measurable marker of the level of potential cardiovascular risk later in life because the levels are both the cause and the consequence of early vascular alterations.

It is now well recognized that vascular phenotype is determined not only by conventional genetic and environmental risk factors, but also by early life programming based on intrauterine fetal growth retardation [1–3]. During childhood, there is a mismatch between the conditions that the fetus is programmed for in utero and the environment that the child meets. Consequently, vascular phenotype is influenced by both size at birth [4] and by weight gain in childhood [5]. Abnormalities in vascular phenotype can be expressed by an increase in BP value, which in this age group is most notable in systolic BP, and also by alterations in vascular elasticity and in the pulse wave reflection. Abnormalities in both vascular elasticity and reflected wave may increase BP values, and vice-versa, creating a vicious circle.

Early vascular phenotypes as a field of study is attracting great interest. These phenotypes can be studied through indirect assessment using non-invasive techniques. Estimations of BP components, pulse wave velocity, and reflecting waves provide valuable information that can be easily recorded and repeated over time. A direct assessment, carried out by looking at the umbilical vessels, can add further valuable information. In this review, we discuss the potential for surrogate markers of early vascular alterations and described the information provided by umbilical cord vessels.

E. Lurbe (✉) · M. I. Torró
Department of Pediatrics, Consorcio Hospital General, University of Valencia, Avda Tres Cruces s/n, 46014 Valencia, Spain
E-mail: empar.lurbe@uv.es

E. Lurbe · M. I. Torró
CIBER Fisiopatología Obesidad y Nutrición (CB 06/03), Instituto de Salud Carlos III, Madrid, Spain

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Surrogate markers of vascular phenotypes

A well-known age-related arterial stiffening process occurs in normal vascular ageing that results from a change in the elastin/collagen ratio due to a reduction in the amount of elastin. Additional qualitative changes also occur in the content of the arterial vessel wall in association with impaired endothelial-mediated vasodilation [6]. These alterations are translated to an increment in systolic BP and in the pulse pressure, which is the pulsatile component of BP, defined as the differences between systolic and diastolic BP [7]. In recent years, other parameters, such as pulse wave velocity (PWV) [8] and augmentation index (AI) [9], have been introduced.

The measurement of PWV is generally accepted as the most simple, non-invasive, robust, and reproducible method with which to determine arterial stiffness [8]. Carotid–femoral PWV is a direct measurement, and it corresponds well to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto–iliac pathway, the carotid–femoral PWV is the most clinically relevant indicator of arterial stiffness, since the aorta and its first branches are what the left ventricle “sees” and therefore are responsible for most of the pathophysiological effects of arterial stiffness. The PWV is calculated as the ratio between the distance covered by the wave and the transit time [10].

The role of wave reflections as an early change in the evolution of vascular disease is being increasingly recognized [9], and the incremental value of the AI, as the estimation of reflecting wave, may be relevant even in normotensive youths. The AI is defined as the difference between the second and first systolic peaks expressed in millimeters of mercury (mmHg) or, alternatively, as a percentage of the pulse pressure (Fig. 1). Although the method has not been validated specifically for children, there are data available that support the validity of the technique in this age group [11]. Vascular properties of the upper-limb vessels vary little with age, in contrast to the changes observed in trunk and lower-limb vessels [12]. The pressure wave forms are recorded from the radial artery of the wrist of the dominant hand with a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX). The wave form data are then processed by the SphygmoCor radial/aortic transform software module (SphygmoCor; PWV Medical, Sidney, Australia) to produce the estimated aortic pressure waveform [12, 13].

Impact of fetal and environmental factors

Early alterations in vascular function have been described in children and adolescents with low birth weight. These alterations are manifested not only through high BP but also through an increment in BP variability [14], pulse pressure [15] and through the impact of reflecting waves on the central pulse pressure [11]. These intermediate phenotypes are the expression of functional or structural abnormalities that have been established from fetal life.

The factors related to the increment of pulse pressure can be studied by using aortic-derived parameters obtained from radial peripheral recordings made using the SphygmoCor system. An inverse relationship between birth weight and AI was observed by Lurbe et al. [11] to be independent of other determinants of wave reflection, with the AI seemingly contributing to the increment in aortic pulse pressure in children with the lowest birth weight. The highest AI suggested a relatively aged arterial phenotype in these children and adolescents, since at the time of appearance, the reflection depended on the pulse wave velocity, which is directly related to the elastic properties of large vessels and less to the peripheral resistance [11]. This observation is in agreement with the results of a previous study in adults which described an inverse relationship between birth weight and PWV, a marker of aortic elasticity and one of the main determinants of reflecting waves [16]. However, in children, there are no differences between groups stratified by birth weight (Fig. 2). This functionally aged phenotype seems to be in accordance with the fetal origin hypothesis of cardiovascular risk, which suggests that intrauterine growth retardation results in a forward resetting of arterial age during extrauterine life [17]. This hypothesis points to the large arteries as the potential origin of a high risk to develop hypertension later in life. These vascular alterations can manifest early in life. After birth, a rapid rise in BP during the first weeks occurs. Children, who at birth had
the lowest birth weight, tend to have not only the lowest systolic BP but also the highest heart rate [4]. This direct relationship between birth weight and BP is promptly blunted during the first month of life since the increment in BP during the first month is inversely related to birth weight: the lower the birth weight, the greater the BP increment.

The greater increase in BP is not solely the result of the rate of growth in children with intrauterine growth retardation. There is abundant evidence suggesting that autonomic regulatory mechanisms, including baroreceptors and chemoreceptors, are important modulators of BP and circulatory function in the newborn. Additional humoral and endocrine factors act directly and indirectly to regulate vascular tone and cardiac function [18]. Changes in autonomic nervous system activity are involved in the development of high BP; however, it is not fully known whether birth weight is associated with the activity of the sympathetic and parasympathetic nervous system [19].

Heart rate increases during the first month. However, in contrast to the BP pattern, heart rate is inversely related to birth weight after birth, and infants with the lowest birth weight have the lowest heart rate increment during the first month. A steep BP increment during the first month of life and the persistence of relatively high BP at the end of the first year indicate that children born with low birth weight are prone to develop a phenotype that may lead to a progressive increment of BP over time.

Umbilical cord, a window to the vascular phenotype?

Both epidemiological and mechanistic studies have supported the notion that vascular and hemodynamic function are at least partially programmed in early life and that this background could play an important role in the process of vascular ageing and arterial stiffening in later life. Consequently, umbilical cord (UC) vessels may be useful in detecting differential phenotypes since vascular wall cells experience the effect of hormonal and hemodynamic changes, which occur during fetal life period.

The study of endothelial and smooth muscle cells from UC vessels can facilitate the search for the alterations involved in the functional vascular changes associated with a lower birth weight. Of the umbilical vessels, the vein is a classic source of both endothelial and smooth muscle cells, mostly because it is a large vessel that can be easily handled [20]. Umbilical arterial vessels, however, have been used less frequently as a source of endothelial and smooth muscle cells since their small diameter make handling difficult [21–23]. The UC is an exceptional source of vascular cells, and these cells offer valuable information on the cellular characteristics of the blood vessels of the individual and their relationship with properties of the vascular system, such as BP.

Comparative studies on the growth characteristics of endothelial and smooth muscle cells from the UC arteries and veins of children born at term revealed that artery endothelial cells obtained from the lower birth weight group exhibit a different cell density and size at confluence from those obtained from children of higher birth weight [24]. Analyses of the proliferation kinetics also showed that the average cell density at confluence of umbilical arterial endothelial cells obtained from subjects with low birth weight is about 1.5-fold higher than that from those of the normal birth weight group. The differences observed in endothelial arterial cells were not present in endothelial cells from the vein nor were they present in smooth muscle cells from arteries or veins (Fig. 3).

The observed differences were not artefactual, i.e. they did not arise as a consequence of methodological bias in cell separation and culture or because of a small number of samples analyzed. The phenotypic identity of a total of 24 endothelial cells and smooth muscle cultures analyzed at passage 2–4 was confirmed using specific molecular markers, and there was no contamination of the endothelial cultures by smooth muscle cells. The relationship between arterial endothelial cell projection area at confluence and birth weight was observed by analyzing cells from 22 individuals, a number of samples which minimizes the odds of obtaining the given results solely by chance.

These above findings need to be considered in the scope of the fetal programming hypothesis [25]. After the initial observation of the effect of intrauterine life on the development of hypertension later in life, an important question arises. What are the mechanisms involved? Although many theories have been proposed, those involving hormonal imprinting [26] and structural changes of
blood vessels and/or kidney [27] have received the most attention. The hormonal imprinting hypothesis has been supported by the demonstration of low activity levels of 11-beta-hydroxyesteroid dehydrogenase along with high levels of fetal cortisol in rats. The consequent increment of fetal exposure to maternal cortisol can produce imprinting patterns of response in vascular structures and cerebral tissue that persist throughout life, with or without structural changes in the vascular tree.

Altered endothelial cell function is a key factor associated with vascular disorders and is critical in fetal growth and development. Pregnancies affected by diseases such as gestational diabetes are associated with human umbilical vein endothelial dysfunction. Functional abnormalities in calcium handling and nitric oxide production have been described in umbilical vein endothelial cells from pre-eclampsia deliveries [28]. These were maintained during culture in vitro and indicate that this may reflect long-term “programming” of the fetal cardiovascular system. If the cell projection area at confluence of the umbilical arterial endothelial cells cultures were to reflect differences that can be found in vivo, the search for a link between birth weight and perinatal—and perhaps adult—BP would be facilitated. The results described herein suggest that, from the four vascular cell types that have been studied, umbilical arterial endothelial cells are a promising candidate in the search for molecular differences capable of explaining the increased risk that lower birth weight individuals exhibit of developing high BP later in life.

**Challenges for the future**

The presence of these vascular phenotype abnormalities may, therefore, be expressions of an “early vascular ageing” susceptibility, because the structural and mechanical properties of the large arteries can be permanently affected by altered hemodynamic stress early in life. If this imprinting exists, it can be present at birth even though the greatest impact comes later in life.

A new understanding of early vascular phenotype has the potential of shifting the focus from traditional blood sampling, aimed at obtaining data on ever-shifting plasma or serum levels of risk factors (glucose, lipids, high sensitivity C-reactive protein), to an evaluation of the target organ damage represented both by properties of the arterial vessel wall itself [29] and cardiac (left ventricular hypertrophy) and renal (albuminuria) involvement [30].
References