

# Vascular Development, Pulse Pressure, and the Mechanisms of Hypertension

Michel E. Safar, Harry Struijker Boudier

**Abstract**—For a given cardiac function, the cyclic blood pressure (BP) curve results from 2 different phenotypes: the mean arterial pressure (MAP), a steady component reflecting the resistance of the microvascular network, and pulse pressure (PP), another component corresponding to large artery stiffness and wave reflections. Around birth, cardiovascular (CV) survival is critically influenced by the coupling between the heart and thoracic aorta, and hence, the adequacy of the Windkessel function, the magnitude of aortic elastin accumulation and the PP level. The maturation of the aortic trunk and its branches results from adaptive mechanisms involving shear and tensile stress, with major potential consequences on heart rate control, transit of wave reflections, and coronary perfusion. An adequate optimization of the Windkessel function, and hence PP, diastolic coronary perfusion and CV survival needs a critical MAP level to be reached in each individual during the postnatal period. The achievement of this MAP level requires the development of multiple resistance segments of the microvascular network, particularly within the kidney. Translated in adult populations, this pathophysiological process gives rise to a Gaussian BP distribution, with individuals remaining in the same BP percentile from birth onward (BP tracking). We suggest that hypertension results from early developmental vascular mechanisms that direct BP toward the higher percentiles of the Gaussian distribution curve. (*Hypertension*. 2005;46:205-209.)

**Key Words:** hypertension, arterial ■ pulse

Many experimental models have been developed to investigate the pathophysiological mechanisms of hypertension in humans. Strong similarities have been observed between spontaneously hypertensive rats and patients with essential hypertension.<sup>1</sup> Both involve a progressive increase of vascular resistance responsible for a parallel increase of systolic blood pressure (BP), diastolic BP, and mean arterial pressure (MAP). However, spontaneously hypertensive rats and hypertensive humans differ substantially by 2 particularities. First, in humans, the BP distribution is Gaussian and unimodal, unlike the 2 distinct populations of genetically normotensive and hypertensive rats. Second, the phenomenon known as BP tracking (ie, that individuals remain in the same BP percentile throughout life), noted previously in hypertensive humans, has not been documented in animal models.<sup>2</sup> Research on the influence of intrauterine conditions on the later development of hypertension has pointed to an important role of early developmental processes.<sup>3</sup>

In this article, we describe some of the early phases of development of the arterial system and delineate under what conditions their investigation may contribute to a better understanding of the natural history and the complications of hypertensive vascular disease.

## Basic Concepts

Endothelial and, to a lesser extent, stem cells, are the primitive precursor cells of the vascular system.<sup>4</sup> The genes that regulate their function are of critical importance to the development of the cardiovascular (CV) system. For instance, cell growth and differentiation are principally mediated by receptor tyrosine kinases.<sup>5</sup> Although the molecular genetics is not the principal goal of this review, it is important to realize that several dominant-negative or null mutations yield lethal but distinct vascular defects and therefore determine very early CV morbidity and mortality. Critical hallmarks of this period are the de novo formation of blood vessels (vasculogenesis) and angiogenesis, the budding of new conduits from pre-existing vessels.<sup>6</sup> These changes require a high degree of endothelial cell plasticity and are generally driven by local mechanical factors and released mediators, as shown by the study of early phases of arteriovenous differentiation.<sup>7,8</sup> These processes are under the control of growth factors, especially vascular endothelial cell and fibroblast growth factors and their receptors.<sup>4</sup>

In 1893, Thoma was the first to show that very early vascular development is extremely sensitive to local hemodynamic forces.<sup>9</sup> He observed that vessels in the area vascu-

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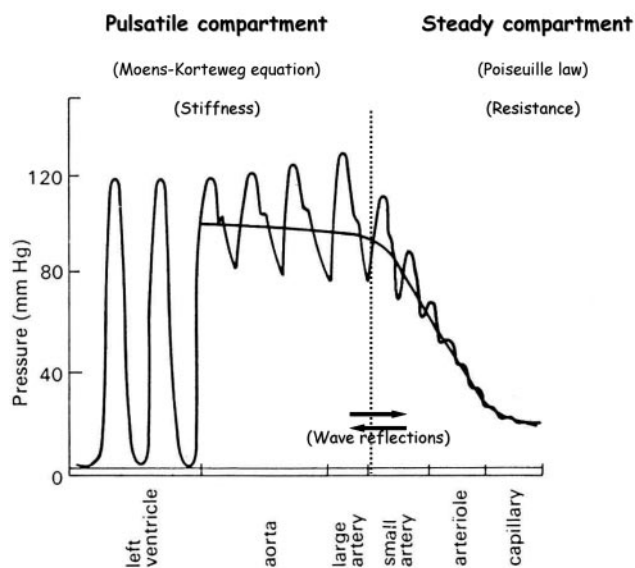
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Pulsatile and MAP pressure within the CV system. The development of an optimal buffering function with a minimal aortic PP needs a given value of vascular resistance and hence MAP. The MAP level is determined by the topography and number of resistance segments composing the microcirculatory network. Wave reflections are the common denominator of the cross-talk between the pulsatile and the steady compartments of the arterial tree.<sup>13,18</sup>

losa of the chick embryo grew rapidly when flow rate was high but regressed when it was low. Similarly, in the arteries of young rats and rabbits, experimentally induced changes of blood flow rates triggered subsequent increases of vessel diameter<sup>10</sup> and accumulation of specific wall constituents.<sup>4,11</sup> Arterial BP increases and also stimulates growth of blood vessels, but wall thickness rather than vessel diameter is involved.<sup>12,13</sup> Because hemodynamic factors provide signals that modulate arterial growth, major changes in blood vessels and hemodynamic function are expected around birth. The particular sensitivity of several CV risk factors such as hypertension to intrauterine conditions may be caused by the major changes taking place in blood vessels in the perinatal period.

The description of mechanical forces within the CV system requires distinguishing between those that are pulsatile and those that are predominantly steady and continuous<sup>13</sup> (Figure). Physiological studies indicate that for a given cardiac function, pulse pressure (PP) is mainly determined by the stiffness of large arteries and the pattern of wave reflections, whereas MAP, the steady component of BP, is influenced by the resistance of smaller arteries and the microvascular network. During the early phase of vascular development, the pulsatile component of BP, which represents a direct continuation of heartbeats, is the predominant module of hemodynamic forces. Through the storage capacities of the aorta, it determines the adequate level of oxygen supply to the tissues. On the other hand, MAP still increases during later phases of development, mainly during completion of the development of microvascular networks at the distal part of the arterial tree.

To understand the role of large arteries in this hemodynamic process, it is important to note that the mechanical

forces derived from aortic elasticity are traditionally described on the basis of 2 different mathematical models: one in the time domain (called Windkessel), and the other in the frequency domain, which involves wave reflections.<sup>13</sup> The former simply advances that the elastic recoil of the aorta enables the cyclic flow coming from the heart to be changed into a continuous flow at the arteriolar (resistant) level. According to Poiseuille's law, vascular resistance, which predominates in the microvascular network, is an important component of this Windkessel model, in which the time constant of the diastolic decay is, by definition, equal to the product of vascular resistance times compliance (elasticity). The frequency-domain model implies that after ventricular ejection and the resulting shock wave initiated at the origin of the thoracic aorta, a forward pressure wave travels along the arterial tree at a given pulse wave velocity. At any structural (eg, elastin or collagen accumulation affecting stiffness) or geometric (vessel branching) discontinuity of the arterial wall, this wave is reflected backward to return toward the heart. Hence, models issued from the frequency domain imply, like the Windkessel model, the presence of a resistance component as a major trigger for wave reflections.

Finally, it appears from these considerations that: (1) an adequate coupling between the heart and the thoracic aorta, and hence an efficient aortic Windkessel function, needs that an optimal level of vascular resistance, and hence MAP should be achieved; and (2) this critical value of MAP results, at the postnatal period, from the development and the specific location of a given number of resistant segments of the microvascular network.

### Functional Coupling of the Heart and the Thoracic Aorta Around Birth

Parturition signals an abrupt change in the growth pattern of large arteries. The most dramatic event results from the cessation of placental blood flow and the initiation of pulmonary gas exchange, leading to independent control of systemic and pulmonary arterial pressures. Another important event is the functional coupling of the heart and the thoracic aorta. At the cessation of placental blood flow, perfusion of many arteries, for example, the carotids and iliacs are approximately halved. This probably reflects the decreased demands for perfusion because arterial  $PO_2$  doubles after lung ventilation starts. However, the largest change seen in a major vessel is a >90% decrease of blood flow in the subrenal abdominal aorta.<sup>14-16</sup> In sheep, this dramatically decreased blood flow is accompanied by a marked reduction of the diameter of the abdominal aorta and a near arrest of wall tissue accumulation that lasts  $\geq 3$  weeks.<sup>15</sup>

Between 1 and 5 weeks postpartum, stroke volume increases in lambs and other species by >2-fold.<sup>16,17</sup> This increased stroke volume would place an increased load on the thoracic aorta, especially in its proximal region, if this vessel did not act as a buffering chamber, storing part of the ventricular stroke volume during systole. During diastole, elastic recoil of the aortic wall propels this volume to the periphery, thereby creating continuous peripheral blood flow and the most adequate oxygen supply. It is worth noting that the Windkessel function of the aorta relies heavily on the low

stiffness and reversible extensibility of this vessel. Low stiffness results in a small PP in the ascending aorta, with average pressure during systole being only slightly greater (10 mm Hg) than the mean cycle pressure and pressure during diastole only slightly less ( $\approx 5$  mm Hg). Thus, an optimal design of the arterial tree is such that the pressure rise during systole is minimized (so that myocardial oxygen demands are minimized) and pressure is maintained as high as possible during diastole (to assure coronary flow). Finally, a rapid perinatal accumulation of elastin is necessary to modulate the Windkessel function of the aorta and accommodate the dramatic postpartum stroke volume increase. This process requires the contribution of vascular smooth muscle (VSM) cells with predominant secretory properties. As shown previously,<sup>18</sup> VSM cells of ectodermal origin and mainly issued from the neural crest are essential for the formation and organization of elastic laminae as well as tenso-receptors of the great vessels.<sup>19–23</sup> Neural crest usually participates in the central control of the autonomic nervous system and of the renin-angiotensin system.<sup>20</sup> Chronic hypoxia of the near-term chick embryo is accompanied by aortic hypertrophy, ventricular dysfunction, and sympathetic hyperinnervation.<sup>21</sup>

In the weeks after birth, arterial growth, and specifically elastin accumulation, correlates with blood flow changes, but a concomitant intriguing flow-independent modulation of arterial growth is seen.<sup>24</sup> This period involves a very rapid aortic elastin and collagen accumulation, independent of blood flow changes. The stimulus that drives this rapid connective tissue synthesis is unknown but serves to preadapt arteries to the large increases of pressure and flow that follow birth.<sup>4,17</sup> Arterial pressures in near-term fetuses are  $\approx 45$  mm Hg, whereas pressure has risen to 65 mm Hg at 3 weeks of age.

The protein product of the elastin gene is synthesized by VSM cells and secreted as a monomer, tropoelastin.<sup>25</sup> After post-translational modification, tropoelastin is cross-linked and organized into elastin polymers that form concentric rings of elastic fenestrated lamellae around the arterial lumen. Elastin-deficient mice die from an occlusive fibrocellular pathology caused by subendothelial proliferation and accumulation of VSM cells in early neonatal life.<sup>26,27</sup> Elastin bears much of the wall tension generated by BP and constitutes a major determinant of resting vessel diameter. Any alteration of genetic origin may be exacerbated by corresponding wall stress and produces, over the long term, arterial wall defects. Experimental reductions of blood flow rates inhibit elastin accumulation in immature arteries.<sup>14</sup> Perinatal elastin accumulation in arteries of lambs correlates with large vessel-specific changes in blood flow rates at birth.<sup>17</sup> Thereafter, reorganization of elastin and its net accumulation continue to be important in arterial remodeling. New elastin is incorporated randomly into lamellae except from some targeting to fenestrae.<sup>28,29</sup> Thus, the development of the buffering function of the thoracic aorta, and hence the accumulation of elastin, are critical points for CV survival around the birth.

Under normal conditions, only 40% to 50% of blood ejected from the left ventricle is stored in capacitive arteries during systole. A decrease of the capacitive properties of the aorta has a well-established negative impact on left ventric-

ular function and coronary perfusion.<sup>13,30</sup> This process, mainly noted in the elderly, is observed in several other conditions, as in young subjects with diabetes mellitus.<sup>30</sup> On the other hand, an abnormal increase of the capacitive properties of the aorta can also have negative effects on CV function. It may be responsible for exaggerated arterial blood pooling during systole, worsening vascular impedance through an increase of the inertial component of cardiac workload, eventually leading to CV death.<sup>13</sup> Such complications may arise very early in life but also are able to develop progressively with time, in association with fatigue of the arterial wall. Two different examples may be given. First, the deleterious accelerations of aging or atherosclerosis are predominantly expressed in central arteries, at the site of heart-vessel coupling and of the thoracoabdominal aorta, whereas distal muscular arteries are much less sensitive to aging.<sup>31</sup> Second, early alterations of the placenta and birth weight may be predictors of future hypertension and atherosclerotic complications during life.<sup>3,32,33</sup>

Together, these findings indicate that: (1) the degree of aortic elastin accumulation at birth influences Windkessel efficiency and thereby the level of aortic PP; (2) the modalities of the Windkessel function require in turn an optimal MAP level,<sup>34</sup> and therefore specific characteristics for the development of small arteries; and (3) such alterations of small arteries, and of microvascular network, are not fully developed at birth and require a maturation of microvessels, which results in a given value of systemic MAP.<sup>34</sup> On the basis of this approach, it is remarkable to observe that adult normotensive and hypertensive populations have exactly the same buffering functions of central arteries under isobaric conditions.<sup>35</sup> These observations explain why it has been proposed that disturbed aortic elasticity may induce the development of chronically elevated BP.<sup>32,33</sup>

### Development of the Aorta and Its Branching Arterial Tree at the Postnatal Period

The aorta is a nonuniform tube that supplies a branched system in which the elastic modulus increases toward the periphery as individual vessel diameters become smaller. During development, this branching process requires significant changes in the cross-sectional area, the wall thickness, and mostly the aortic length, which play an important role in the heart rate control.<sup>13</sup>

During late development and in adults, chronic changes in blood flow rates cause corresponding changes in arterial diameters, whereas pressure increases cause wall thickening. By these means, the vessel structure continually adapts to changing hemodynamic loads. This remodeling is regulated by direct sensitivity of vascular tissues to fluid shear stress in the case of flow and to tensile stress in the case of pressure.<sup>13</sup> The roles of shear and tensile stress in vascular development have been extensively reviewed previously.<sup>4,13</sup>

The postnatal increase of collagen, and especially collagen cross-linking, principally affects the abdominal aorta and its branching system. During postpartum, collagen enables tissue adaptation to the increased tensile stress. It is remarkably well suited to carry out this role because of the extraordinary tensile strength and stiffness of its fibrils, properties that are

largely attributable to strong axial and lateral bonding afforded by intermolecular and intramolecular cross-links. These links are important stabilizers of the fibrils. They prevent slippage of adjacent molecules under applied tensile stress<sup>36,37</sup> and contribute to the yield stress and ultimate tensile stress (strength) of the collagen matrix. Strong correlations between intermolecular cross-linking and tensile strength have been demonstrated in skin, tendon, and bone.<sup>38</sup> A postnatal increase of intermolecular collagen cross-linking serves to resist the concomitant 143% increase of physiological aortic wall stress.<sup>39</sup> In contrast, a progressive or acute reduction in cross-linking might precipitate CV complications.

Aortic length follows the dimensions of contiguous tissues during development and, within some limits, remains constant in adults. During childhood, such arteries are normally subjected to considerable lengthwise stretch *in vivo*.<sup>31</sup> If newly synthesized tissue is produced in the longitudinal direction at any site along the vessel length, then the remainder of the vessel can retract slightly under the elastic forces that impose longitudinal stretch. Because vascular tissues are incompressible, the retraction must be isovolumic. As a result, the thickness or circumference of the artery wall will increase.<sup>40</sup> With the development of the branched system, the increased vascular resistance is more and more determined by vessel caliber and therefore involves more and more arterial wall discontinuities, an important aspect for the development of wave reflections and therefore for the adequation of coronary perfusion.<sup>13,18</sup>

Through the branching of the arterial tree, the *in vivo* hemodynamic status is progressively composed of a complex network of small arteries and arterioles that characterize the resistance vasculature. According to Poiseuille's law, a higher minimum vascular resistance could result from a combination of reduced lumen diameter of individual vessels, vessels growing longer, or their rarefaction (a decreased number of vessels connected in parallel).<sup>41</sup> Traditional experiments have shown that minimum vascular resistance is increased by 37% in established hypertension.<sup>34</sup> Vascular resistance changes abruptly over the short length of the vessel pathway between arteries and veins, and this has important consequences.<sup>13</sup> First, the very high resistance over a short distance causes MAP to fall precipitously over this short length. Second, suddenly high resistance impedes pulsatile phenomena and steady flow so that theoretically, the amplitude of PP falls concomitantly with MAP, resulting in steady flow through these resistance vessels. Third, and most important, arterial pulsations that cannot enter the high-resistance vessels are reflected and join with pressure waves approaching the high-resistance vessels. Finally, resistance vessels not only contribute to control the capillary pressure but also participate to the occurrence of wave reflections.

An important aspect of these observations is to elucidate under which conditions the development of the microvascular network may affect the resistance properties of the vascular system and hence may determine exactly the MAP level.<sup>41,42</sup> We learned from the Poiseuille's law that the length, the radius (to the fourth power), and the thickness of the arteries are the most important geometric factors determining the

individual resistance of a given vessel. However, for a tree-like network, the number of blood vessels connected in parallel is another important factor to consider. Computer studies have shown that elimination of a number of small arterioles from a vascular bed (rarefaction) causes an increase of total vascular resistance.<sup>43</sup> The more complex situation to elucidate is that of arcade-like networks, which contain in-series- and in-parallel-coupled arteriolar branches. In these networks, the lengths and diameters of individual arterioles, their branching angles, the location of the branching points, and the number of branches all contribute to resistance.<sup>42</sup> This situation implies that the nature of the change of the network must be defined in addition to the absolute number of blood vessels. Finally, a given degree of microvascular development corresponds to a given level of vascular resistance and hence a given level of MAP, which will contribute to an optimal oxygen supply to the tissues and to an adequate aortic buffering function. Finally, throughout vascular development, it is conceivable that apoptosis or hypertrophy of VSM cells could be independently at work in various vascular territories to maintain optimal levels of vascular resistance and MAP during adulthood.<sup>44</sup> Furthermore, some organs, such as the kidney, might be particularly specialized in all these process. Accepting this hypothesis, it seems likely that rarefaction of the microvascular network, particularly regarding the nephrons number, may be a major mechanism initiating hypertension.<sup>45</sup>

### Prospective Views and Conclusion

Structural modifications of small arteries or rarefaction of microvessels are strongly associated with hypertension and traditionally considered to be responsible for high MAP. Throughout this review, we proposed another possibility: a given level of MAP, and hence a given degree of microvascular network development, is required to optimize aortic Windkessel function. This approach may explain why, in a large population with a given genetic and environmental background, a Gaussian BP distribution is observed and therefore concords with the phenomenon of BP tracking, which is commonly observed in human populations. This pathophysiological mechanism, which fits with the predictive value of PP and arterial stiffness on CV morbidity and mortality, is strengthened by 3 recently published findings. First, structural alterations of small artery walls are a significant CV risk factor in hypertensive subjects but in association with increased PP.<sup>46</sup> Second, early wave reflections and increased aortic stiffness, the 2 main determinants of PP, are also significant independent CV risk factors, more prominent than PP itself.<sup>42,47</sup> Finally, central PP is a stronger CV risk factor than brachial PP, particularly for the prediction of myocardial infarction.<sup>48</sup> Such epidemiological findings strongly suggest that disturbed heart-vessel coupling and Windkessel function, 2 major events of CV development at birth, are important and independent determinants of future CV, and mainly coronary, complications.

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