Function–structure relationship of elastic arteries in evolution: from microfibrils to elastin and elastic fibres

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Summary
Evolution of species has led to the appearance of circulatory systems including blood vessels and one or more pulsatile pumps, typically resulting in a low-pressurised open circulation in most invertebrates and a high-pressurised closed circulation in vertebrates. In both open and closed circulations, the large elastic arteries proximal to the heart damp out the pulsatile flow and blood pressure delivered by the heart, in order to limit distal shear stress and to allow regular irrigation of downstream organs. To achieve this goal, networks of resilient and stiff proteins adapted to each situation — i.e. low or high blood pressure — have been developed in the arterial wall to provide it with non-linear elasticity. In the low-pressurised circulation of some invertebrates, the mechanical properties of arteries can almost be entirely microfibril-based, whereas, in high-pressurised circulations, they are due to an interplay between a highly resilient protein, an elastomer in the octopus and elastin in most vertebrates, and the rather stiff protein collagen. In vertebrate development, elastin is incorporated in elastic fibres, on a earlier deposited scaffold of microfibrils. The elastic fibres are then arranged in functional concentric elastic lamellae and, with the smooth muscle cells, lamellar units. The microfibrils may also play a direct functional role in all mature arteries of high- and low-pressurised circulations. Finally, since blood pressure regularly increases with developmental stages, it appears possible that the early deposition of microfibrils, which are highly-conserved in evolution, corresponds, at least in part, to an early microfibril-driven elasticity in low-pressurised arteries, present across species. In vertebrates, when pressure developmentally rises above a threshold value, the vascular wall stress may turn on the expression of other resilient protein genes, including the elastin gene. Elastin would then be deposited on microfibrils and resulting in the elastic fibre network and elastic lamellae whose mechanical properties are adapted to allow for proper arterial work at higher pressures.


L’évolution des espèces a conduit à l’apparition de systèmes circulatoires incluant des vaisseaux sanguins et une ou plusieurs pompes pulsatiles. Le résultat consiste généralement en une circulation ouverte à basse pression chez la plupart des invertébrés et en une circulation fermée chez les vertébrés. Dans les deux cas, les grandes artères élastiques proches du cœur amortissent la pression et le flux pulsatiles cardiaques, afin de limiter les forces de cisaillement du flux distal et de permettre une irrigation plus régulière des organes. Pour cela, les parois artérielles contiennent des réseaux de protéines élastiques et de protéines plus rigides, adaptés à chaque situation (pression sanguine forte ou faible), qui confèrent aux artères une propriété d’élasticité non linéaire. Dans la circulation à faible pression de certains invertébrés, les propriétés mécaniques artérielles peuvent être dues en quasi-totalité aux microfibrilles. En revanche, dans les circulations à haute pression, les propriétés

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Evolution of species has led to a tremendous diversity of animal adaptations to their environments. The necessity of fluid, nutrient, oxygen and signalling molecule transports emerging in increasingly complex organisms resulted in the appearance of a cardiovascular system, except in the most primitive unicellular and pluricellular organisms. Different functional requirements led to evolution of different types of hearts and different types of hemolymph or blood vessels. Therefore, the functional interrelations between heart, vessels and blood or hemolymph, although conceptually similar, are physically quite different across the species. Of course, functional differences paralleled structural differences of cardiovascular tissues. In blood vessels, several types of resilient extracellular matrix proteins have appeared during evolution, adapted to each species, in order to allow the arteries to smooth the pulsatile flows of different natures imposed by the heart, and therefore properly irrigate the organs. The purpose of the following is to review the potential link between the different types of cardiovascular systems, the related biomechanical requirements of the blood vessels, and the structural and mechanical properties of the corresponding resilient proteins in the vascular walls.

**EVOLUTION OF THE CARDIOVASCULAR SYSTEM: TOWARDS HIGH PRESSURE CIRCULATION**

In unicellular or primitive pluricellular organisms, the small size of the entire organism allows a relatively easy distribution and exchange of vital substances, such as O₂ and CO₂, and nutrients, because each cell of such organisms is located in direct or quasi-direct contact with the extracellular medium. In this condition, transfer of gases or small molecules from the intracellular space to the environment, or from the environment to the intracellular space, is regulated by simple diffusion or by direct action of membrane transporters. During evolution, the survival of some organisms in various conditions was made possible because of the association of several cells, such as identical-cell-type aggregates or association of differently specialised cells, allowing a more efficient function of each cell type, such as in the first real pluricellular organisms. Of course, such evolutionary cell association has been permitted and paralleled with the appearance and evolution, in vertebrate then in vertebrate, of a complex extracellular matrix allowing adhesion and communication between cells [1]. Further evolution gave a selective advantage to ever bigger (with more cells) and more complex (with more functions) organisms, with specialised and localised organs, leading to plants or animals whose big sizes prevented the most internal cells from having direct exchanges of substances with the environment, because of the long distance between these two media. To remedy this difficulty, fluid mobilisation systems have experienced parallel evolution, allowing the presence of always renewed internal fluid at the interface between internal and external fluid, therefore exchanges between the inside and the outside and between organs. For this purpose, a confined liquid compartment progressively took place: the circulatory system, a vessel network permitting long distance transport of substances between internal cells and organs and zones specialised in the exchanges with the external medium. Mobilisation of circulatory fluid (blood or hemolymph) was made possible by the progressive differentiation of contractile vascular portions or the appearance of a specialised organ (unique or not): the heart. First communicating with the extracellular medium, the ‘open’ circulation allowed mobilisation of both circulatory fluid and extracellular medium, under a low pressure because of the low hemodynamic resistance of the terminally open vascular network. In more higher species, the increase in size and in the number of very specialised organs gave rise to an ever increased...
need for a huge vascular network, branching from a few large vessels to many small vessels (capillaries), therefore dramatically increasing the hemodynamic resistance. The parallel response of evolution was to close the circulatory system and increase the heart efficiency, allowing a rise in initial circulatory fluid pressure, therefore a chance for this fluid to circulate. Moreover, a higher pressure maintained the vessels distended, contributing to decrease the hemodynamic resistance. Also, the exchange mechanisms between the circulatory fluid and the external medium were improved by this pressure rise, resulting in a high hydrostatic pressure gradient facilitating some transmembrane or transcellular exchanges, such as in the renal function. These evolutionary events eventually resulted in the vertebrate circulatory system, i.e. closed and under a high pressure [2, 3].

**MECHANICAL FUNCTION OF ARTERIES**

Hemodynamic resistance of the arteries leads to a progressive decrease in blood pressure along the vascular tree, from the heart to the irrigated organs. In order to counteract the effect of higher pressure and to maintain general integrity of the vessel, most blood vessel wall include circumferentially oriented collagen fibres, at least in their external part. Collagens are a family of proteins which are able to interact and form fibres which are stiff and poorly resilient (high elastic modulus), therefore adapted to limit the circumferential extension of the vessels under pressure. The collagen fibre network is adapted to be efficient at the maximum physiological blood pressure of each species, and even higher. Nevertheless, presence of collagen fibres is not sufficient to allow proper function of arterial walls. As a matter of fact, all existing blood pumps — different types of hearts, contractile vessels, etc. — produce cyclic increases and decreases in pressure, resulting in generation of a pulsatile flow. Therefore, when leaving the pump, the flow would be pulsatile, not constant, all along the circulatory tree if it was injected in simple tubings, with increased shear stress and irregular organ irrigation (Poiseuille’s law stating that flow is a linear function of pressure variation). In order to avoid that, a compensatory arterial property (elasticity or viscoelasticity) and function have evolved parallel to the evolution of the heart. The proximal arteries circumferentially (and to a lower extent longitudinally) distend when the high pressure flow leaves the heart (systole) and resilient proteins of the vessel wall temporarily store this stretching energy. When the pump cycle is at the low pressure point (diastole), the elastic arteries release this energy by compressing the contained blood while returning to their initial size, therefore maintaining a rather high diastolic blood pressure in the vessel. The consequence is that the pressure does not decrease in the vessels as much as in the heart ventricles during the diastole, hence the pressure variations in the arteries during the cardiac cycle are of relatively lower amplitude, distally resulting in a more constant flow and organ irrigation. This is of extreme importance and induces dramatic difference between heart and aorta diastolic pressures in some species: for instance in humans, the systolic/diastolic pressure (mmHg) in the heart left ventricle is in the range of 120/5, whereas it stays at about 120/80 in the aorta! This mechanical phenomenon, commonly known as the Windkessel effect, is mostly present in arteries proximal to the heart: the large elastic arteries, so called because of a wall content rich in resilient protein and poor in muscular cells, such as the aorta. This simplest model of Windkessel effect has to be completed in mammal elastic arteries, and not in lower vertebrates and invertebrates, by a complex interaction between the wall structure and successive pressure waves produced by the heart. Some waves are simply transmitted downstream in the walls whereas some other pressure waves are reflected back (upstream) towards the heart, the result of these interferences being a modification of hemodynamic parameters, therefore an additional source of regulation of the blood flow [4, 5].

Meanwhile, the more distal and smaller arteries, called muscular arteries because of a vascular wall content poor in resilient proteins and rich in smooth muscle cells, receive an already-smoothed blood flow from the elastic arteries, and have a more limited dampening action but regulate blood flow through active constriction or dilation [5, 6]. The following will mostly describe the phenomena due to and taking place in elastic arteries.

The necessities of such a vascular system directly require very special mechanical properties of the resilient proteins from the elastic artery walls, resulting from the circumferential and longitudinal structural arrangement of these proteins and other wall components. The requirements are not the same when the pressure and pressure variation amplitude are low, such as in invertebrates and lower vertebrates, or higher, such as in most vertebrates. In the later case, the vessels and wall proteins have to resist intense stretch forces due to high pressure, but they still have to present the above described elastic properties. As a consequence, different types of resilient proteins appeared during evolution, with properties adapted to the precise requirement of each organism vasculature and blood pressure.

**INVERTEBRATES AND PRIMITIVE VERTEBRATES — LOW BLOOD PRESSURE**

Circulatory fluid (blood or hemolymph) pressure as well as pressure variation amplitudes are generally low in invertebrates and some primitive vertebrate arteries, mostly ranging from one or a few mmHg up to 20–30 mmHg. For instance, in a variety of invertebrates, the arterial pressure (systolic/diastolic or mean, in mmHg) is in the range
of 5 (systolic: 8) in the crab [2, 7], 1.9/0 in the mussel, 6/2 in the locust, 3/1 to 16 in the lobster depending on animal activity and the reports [2, 3, 8]. Mean blood pressures are in the range of 30–60 and 19 mmHg in the primitive vertebrates (jawless fishes) lamprey [9] and hagfish [8] respectively, although, low systolic/diastolic pressure variations would be sufficient to result in irregular flow and organ irrigation if the vessels had not adapted to smooth the blood flow. Arteries of these animals are composite materials made of cells, in particular fibroblasts and muscle cells, and extracellular matrix, including collagens, but do not contain elastin [10–15].

A series of investigations have been performed on the elastic properties of arteries from different invertebrates (lobster, crab and whelk) as well as from some primitive vertebrates (lamprey and hagfish), all lacking elastin, the major resilient protein found in most vertebrates [9, 10]. Interestingly, these vessels exhibit mechanical properties adapted to low pressure and low pressure variations, allowing a Windkessel effect-like phenomenon to take place [9, 10]. From comparative experiments performed on cannulated aortae from these different species, the pressure-volume relations show that these vessels present elastic properties in the range of the physiological low blood pressure level of each species [10]. These elastic properties are non-linear since the arterial volume, after increasing regularly, tends to plateau when the rising pressure reaches a certain value above normal. The maximum increase in arterial volume, as compared to resting volume, is of at least two fold (up to 5.5 fold in the crab), except in the whelk (1.7 fold) (figure 1). In other words, the vessels become stiffer at higher pressure. Non-linearity is associated with the vessel dual function of elasticity (low stiffness below and at physiological pressure) and protection (high stiffness above normal range of pressure to avoid vessel damage or rupture). The same non-linear elastic properties are also found in a variety of other invertebrates including a different species of crab, squid and octopus [16–19].

Also, the cycles of increasing-decreasing pressure applied to the arteries show that the curve representing the return to minimal volume (from maximal volume) is lower that the curve representing the rise from minimal volume to maximum volume (presence of hysteresis). Hysteresis, the difference in the areas under the two curves, is a usual phenomenon of vessel mechanics resulting from the loss of energy between its storage by the artery (while pressure increases) and its release (while pressure decreases): the lower hysteresis is, the more efficient the vessel is. In the case of these animals, hysteresis ranges from 13–18% (lamprey, hagfish and lobster) to 25–30% (crab and whelk), which is rather low and comparable to the values obtained in vertebrates (see below). These results clearly indicate that, in invertebrates and primitive vertebrates, the aorta wall structure contains materials allowing a high amplitude distensibility adapted to low pressure increments, and also that these materials allow the aorta to damp out the blood pressure fluctuations generated by the heart cycle. Light microscopy as well as electron microscopy show that the arterial wall of these animals is a composite material, organised in two to three layers (laminae), each one containing different proportion of cells and extracellular materials. Endothelial cells are confined to the luminal side of the wall (intima), whereas smooth muscle cells are arranged rather in the medial part (media), and fibroblasts are sometimes present in the outer lamina (adventitia, when present) together with collagen fibrils. In the extracellular matrix fibres, no elastin is present, and collagen fibres or fibrils are present mostly in the external parts of the wall, whereas acid proteoglycans are present mostly in the internal and medial laminae. In addition, except in the whelk, abundant oxytalan-like networks of microfibrils, with diameters of: 20–35 nm in the lobster, 20–25 nm in the crab [10], 11–17 nm in the lamprey and hagfish [9, 20] are also contained mostly in the medial laminae, together with smooth muscle cells and microfibrils. The microfibrils, quantitatively one of the principal structural component of the wall, present a significant waviness and have a beaded appearance with a 40–52 nm periodicity in the lobster, unclear periodicity in the lamprey, and no periodicity in the crab [9, 10]. Functionally, further experiments performed on lobster aorta segments showed that the elastic properties of this artery are almost entirely due to the action of microfibrils, resulting from two different phenomenon depending on the pressure level. At the lowest pressures, reorientation/alignment of initially wavy microfibrils seem to take the load and provide the artery with its general elastic property. At higher pressure, therefore higher strains (above 80%), it is deformation/elongation of the microfibrils which takes the load and eventually limit vessel distension [21, 22], unlike in vertebrate vessels where collagen plays this limiting role [23–25]. When the lobster aorta is stretched, the microfibril bead periodicity increases from 43 nm (unstretched) up to 58 nm, before returning to resting length when stretch ends [21]. In the physiological range of blood pressure of each species, the circumferential elastic modulus (parameter representing the stiffness) of the aorta is 0.03–0.09 MPa (except in the whelk: 0.15 MPa), whereas the elastic modulus of microfibrils is in the range of 1 MPa [21], which is close to the elastic modulus of elastin (0.1–1.2 MPa), and commonly in the range of 0.4 MPa [26–28].

It is known that microfibrils play a role in vertebrate elastic fibre development [29], therefore leading to developmental pathologies, such as Marfan syndrome, when genetically altered [30]. Also, it was shown that fibrillin-rich microfibrils of several other species (at least bovine and from sea cucumber) are resilient, through the study of the mechanical properties of contained fibrillins, and that reorientation and elongation of fibrillin
Figure 1. Pressure-relative volume curves obtained at 10°C from (excised) cannulated aorta segments proximal to the heart from two primitive vertebrates: lamprey (A), hagfish (B), and from three invertebrates: lobster (C), horseshoe crab (D) and whelk (E). Upper curves represent the pressure-relative volume relation during vessel inflation with saline solution at increasing pressures, whereas the lower curves represent the pressure-relative volume relation during vessel deflation (decreasing pressures) immediately following inflation. Relative volume is the ratio of instantaneous volume to initial volume, the latter being the volume at the pressure at which the measurement was started. When applicable, open squares represent the mean resting blood pressure in each species. Two open squares indicate the blood pressure range. Reprinted from Davison IG, Wright GM, DeMont ME. The structure and physical properties of invertebrate and primitive vertebrate arteries. J Exp Biol 1995; 198: 2185-2196, copyright © The Company of Biologists Limited 1995, with kind permission from The Company of Biologists Limited, Cambridge, United-Kingdom.
under stretch results in significant molecule extension and bead periodicity increase [31 – 33]. The microfibril-driven mechanics of invertebrate arteries suggest a more general and important direct mechanical role in arteries for microfibrils (and for their major component: fibrillins) which appear to be highly conserved throughout evolution from invertebrates, like the jellyfish, to mammalsians [34]. Microfibrils could play a direct functional role even in elasticity of vertebrate blood vessels, which also contains microfibrils.

A SPECIAL CATEGORY: THE INVERTEBRATES WITH HIGHER BLOOD PRESSURE

Only a few invertebrates present a high blood pressure. Most of these animals have a closed — or virtually closed circulatory system, and high blood pressure is responsible, in some cases, for movement or posture (hydrostatic skeleton) rather than for the necessities of organ irrigation per se [35]. In the earthworm, the systolic/diastolic blood pressure values are 48/34 mmHg [3]. These values can be modulated by body muscle contraction that this species uses to compress body cavities and cavity fluids, including vessels and blood. This process results in increased body cavity rigidity and, therefore, produce cavity extensions and movement of body segments. A second example is found in the arthropods. Certain spiders use increases in leg blood pressure to produce sudden extension of the leg segments, which generates jumping. In these spiders, arterial blood pressure could rise up to 400 mmHg [3, 36, 37]. In other invertebrates (cephalopods), the high blood pressure seems to be related to their high organisation and specific requirements, for example respiration and renal activity. In octopus and squid, which have a highly developed closed circulatory system, blood pressures potentially as high as 75 mmHg have been observed during activity [35, 38, 39], and in the octopus, systolic/diastolic arterial blood pressure is in the range of 60–40/40–18 mmHg [3, 18, 35, 40].

Little is known about the structure and mechanics of the arteries of most these high blood pressure invertebrates. Nevertheless, in addition to collagen and microfibrils, it is known that the octopus has developed a specific arterial resilient elastomer, different from elastin, present in significant amount in the aorta. Isolated fibres of this elastomer have an elastic modulus of 0.4 MPa, in the range of the elastic modulus of elastin fibres [26 – 28]. The elastomer endows the octopus arteries, at least the aorta, with non-linear elasticity with maximal volume-per-length increase of five fold between the unpressurised vessel to above physiological pressure, or two fold within the the physiological pressure change within the cardiac cycle (40/18 mmHg). The presence of the elastomer results in an aorta circumferential elastic modulus of 0.01–0.1 MPa in the physiological range of blood pressure. The elastomer is also arranged into fibres that work efficiently at physiological high blood pressure, resulting in the presence of an arterial ‘elastic reservoir’, or Windkessel-like effect [18, 19]. Other invertebrates, with high or low blood pressure, are known to have developed elastic/rubberlike proteins, such as abductin in mollusces [41, 42] or resilin in arthropods [43 – 45], but no clear relationship is established between these proteins and vascular mechanics.

LOWER AND HIGHER VERTEBRATES, MAMMALS: HIGH BLOOD PRESSURE AND MATUERE ARTERY FUNCTION

Vertebrates generally present a blood pressure higher than in invertebrates and primitive vertebrates, ranging from 20–30 mmHg to 200 mmHg or higher for some of them. The blood pressure range is generally even higher in homeothermic — or warm-blooded — animals (higher vertebrates: most mammals and birds) than in poikilothermic — or cold-blooded — animals (lower vertebrates: fishes, reptiles, amphibians). For instance, in mammals, the systolic/diastolic (or mean) arterial blood pressure (mmHg) is in the range of 100 in the fin whale [46], 240/180 in the giraffe, 120/80 in humans [2, 3], 90 in dogs [47], 68 in sheep [48], 128/98 and 105–110 (mean) in pigs [49], 130–128/95–75 [50, 51] or 82–116 (mean) [4, 52, 53] depending on the strain in rats, 108/75 (mean) depending on the reports in mice [54]. In birds, the blood pressure is in the range of 135/120 in the chicken, 180/135 in the sparrow and starling, 135/105 in the pigeon, 162 in the duck and 193 in the turkey [55]. In reptiles, lower arterial mean blood pressures (mmHg) have been found in the range of 23 in the lizard and 33 in the garter snake [4], and, in amphibians, the systolic/diastolic pressure has been measured in the range of 30/20 in the frog [3] and 23 in the toad [4]. Finally, fishes present huge species-dependent blood pressure differences, ranging from about 10 mmHg in a few species, such as Scyliorhinus canicula, up to 75 mmHg or higher (potentially 120 mmHg) in the Chinook Salmon, but values of 20–50 mmHg are the most common, like in the catfish (40/30) or the eel (35–40, possibly up to 60, syslogic [2, 56].

Arterial elasticity of mammals has been studied for decades. The first serious and rigourous assessments were probably the experiments performed by Roy in the late 19th century through experiments based on extended strips or excised cannulated segments of different artery types excised from different mammals of relatively big size (cat, rabbit, dog, human, etc.), healthy or ill, or from ‘fresh’ human dead bodies of different ages. As early as 1880–1882, Roy concluded, using other terms, that arteries exhibit non-linear elasticity of arteries, meaning that
Figure 2. Pressure-relative volume curves obtained at room temperature from (excised) cannulated aorta segments distal to the aortic arch from three different lower vertebrates: toad (A), lizard (B), snake (C), and one mammal: the rat (D). Upper curves represent the pressure-relative volume relation during vessel inflation with saline solution at increasing pressures, whereas the lower curves represent the pressure-relative volume relation during vessel deflation (decreasing pressures) immediately following inflation. Relative volume is the ratio of instantaneous volume to the unpressurised vessel volume. Arrows along the pressure axis represent the mean resting blood pressure in each species. Arrows and percentages on the curves represent the hysteresis value in each species. Reprinted from Gibbons CA, Shadwick RE. Functional similarities in the mechanical design of the aorta in lower vertebrates and mammals. Experientia 1989; 45: 1083-1088, copyright © Birkhaüser Verlag Basel 1989, with kind permission from Birkhaüser Publishing Ltd. Basel, Switzerland.

Arteries are most circumferentially distensible at low or physiological blood pressure and distensibility is considerably lower at high pressure. The maximal distensibility is found around the physiological blood pressure range, and illness or aging decrease arterial extensibility [57]. While followers refined these results in humans and other mammalians — such as rat, pig, dog and rabbit — [4, 47, 49, 58–61], little has been shown about arterial elasticity in other, in particular lower, vertebrates. However, experiments have been performed to compare the arterial distensibilities from the lower vertebrates amphibian (toad), and reptile (lizard and snake), with mammal (rat) (figure 2) [4]. Again, these findings showed that cannulated arteries of all tested lower vertebrates (toad, lizard and snake) and mammals (rat) are highly distensible and non-linearly elastic, and that the distensibility at high pressure is lower than at lower pressure. With pressure increasing up to above physiological pressure ranges, the maximum increase in aorta volume before plateau (as compared to unpressurized artery volume) was in the range of 3–3.5 fold in rats, toad, snake and lizard [4], 4–6.5 in the rabbit [57, 61], 5.5–6 in the cat [57], 5 in the dog [47, 57], ≈2.5 in pigs [49] and 2.5–4 in middle-aged humans, depending on age [59], as compared with the
2.5 fold increase in arterial volume in the primitive vertebrates lamprey and hagfish and, in invertebrates, 4.5–5.5 fold in the lobster and horseshoe crab and 1.7 fold in the whelk [10]. The circumferential elastic moduli (representing arterial stiffness) at physiological blood pressure can be estimated from isolated and cannulated aorta volume (or diameter)–pressure curves and wall thickness in the physiological blood pressure range. These experiments allow calculation of a circumferential elastic modulus in the range of 0.75 MPa and 1.7 MPa in thoracic aortae from young (11–20 years old) and older (36–52 years old) humans, respectively [62], 0.74 in the thoracic aorta of dogs [47], 0.32 MPa in the sheep [48], 0.27 MPa (cannulated) or 0.67 MPa (in vivo) in the porcine abdominal aorta [49]. Hence, the elastic modulus at physiological intraluminal pressure is in the same range in a broad variety of elastic arteries, since it has also been determined in the range of 0.89 MPa in the cannulated dog carotid arteries [63] and, in a diving mammals such as the fin whale, the aortic arch elastic modulus is found close to 0.4 MPa whereas the elastic modulus of the thoracic aorta is higher, near 12 MPa [46]. Also, in a series of experiments performed in the range of the physiological blood pressure of each species on isolated cannulated aorta segments from lower vertebrates and mammals, the circumferential elastic moduli were 0.33, 0.30, 0.51, 0.5 MPa in the toad, the lizard, the snake and the rat, respectively [4]. These values are about ten times higher than the circumferential elastic moduli of the aorta found in invertebrates, when measured in the physiological range of blood pressure of each species: 0.03–0.09 MPa in the lobster, crab, lamprey and hagfish (except in the whelk: 0.15 MPa) [10]. However, the efficiency of storage–release of energy by vertebrate arteries is not better than that of invertebrate arteries. Hysteresis values are 17% in the toad, 19% in the lizard and 25% in the snake, therefore very comparable to the values found in invertebrates. Only the rat aorta seems to be slightly more efficient, with a hysteresis in the range of only 8% [4].

No dramatic difference is then observed between the maximal distensibility and efficiency of aortae from invertebrates to mammals, working in different physiological blood pressure ranges and with different distensibilities. When the volume-per-unit-length changes of isolated aorta are taken between the limits of the estimated diastolic — systolic blood pressure range — i.e. during the cardiac cycle of each species, the volume changes are in the range of 20–50%. In particular, the change is between 50% in 20 years old and 20% in 50 years old human [59] and ≈10% in pig [49] aortae.

Nevertheless, these absolute distensibility values have to be interpreted with caution since they were obtained on excised cannulated arteries in the absence of the vessel environment in vivo, therefore only describing the mechanical properties of the isolated vessel. The effective mechanical properties of the elastic arteries in situ (closely surrounded by physically related tissues) are composed of the intrinsic properties of the artery cumulated with the effect produced by the tethering of the surrounding tissues. Moreover, in vivo, the blood pressure level is cyclic, stays in a narrow interval, and does not rise as high as in these ex vivo experiments. To evaluate the in vivo/isolated vessel difference in arterial distensibility, measurements have been performed in vivo, using a differential transformer or ultrasound devices. These experiments estimate relative volume-per-unit-length (adapted from diameter measurements) variations during cardiac cycle — i.e. systolic to diastolic pressures — from less than 5% percent in the dog and rat carotid artery [51, 64] to ≈25% in the human carotid artery and the porcine abdominal aorta [49, 65]. In the case of the porcine abdominal aorta, the difference between isolated and in situ aorta volume increase during cardiac cycle-like pressure variation is striking: from 10 to 25%. This is due to the fact that, in the absence of the tethering of the surrounding tissues, isolated arteries are more distended at low pressure so that they present a higher diameter and are stiffer, as compared to in vivo, in the physiological blood pressure range [49]. The same is true in (other) human arteries [58]. These findings show that, whereas experiments performed on isolated vessels can provide good results on pure biomechanics of the vessel wall, trying to directly generalise these results to the in vivo situation could lead to misinterpretation of the physiological phenomena.

A prime particular case is the muscular arteries, distal to the proximal elastic arteries, where non-linear elasticity is also found. Similar experiments were performed on excised cannulated muscular arteries where intraluminal pressure is increased to a above-physiological pressure level (up to 200 mmHg) to reach a plateauing diameter. Volume increases, as compared to unpressurised volumes, are in the range of 4, 1.8 and 2.9 fold (1.1–1.3 fold only in the systolic/diastolic range), whereas circumferential elastic moduli (at physiological blood pressure) calculated from diameter or volume values are in the range of 0.25, 1.7 and 1 MPa in rat uteroplacental (radial) artery, dog basilar artery and rat mesenteric arteries, respectively [66–68]. Also, in rat mesenteric arteries in situ, the same increase in pressure results in a similar 2.7 fold increase in volume, whereas incremental elastic modulus at physiological pressure, estimated from [50], is again in the range of 1 MPa. Therefore, it seems that there is little difference in mechanical properties between isolated cannulated and in situ muscular arteries, unlike in elastic arteries.

A second particular case is that of the arteries found in the low-pressurised pulmonary circulation of aerial vertebrates (≈10–20 mmHg). In adult animals, because of a low resistance of the vascular tree, a low pressure and low amplitude of the blood pressure cycle and thin arterial walls are sufficient to ensure the function of these arteries [35]. Nevertheless, the property of non-
linear elasticity is also found in the pulmonary arteries, which store at least 15–20% of the right ventricle stroke volume during systole before releasing it during the diastole, therefore dampening the arterial blood flow [69]. Like in the systemic circulation, pulmonary elastic arteries are distensible: as compared to the volume in unpressurised arteries, the approximate volume-per-unit-length can increase up to 1.2 fold at physiological intraluminal pressure (circumferential elastic modulus close to 0.2 MPa) up to a maximum of 1.4 fold at high pressure in situ in the proximal intra-pulmonary arteries of mature pigs [70], and 1.7 fold at physiological pressure (circumferential elastic modulus close to 0.1 MPa) up to a maximum of 4 fold in cannulated left pulmonary arteries of adult mice (personal unpublished data). In humans, in vivo, the volume-per-length of the large elastic pulmonary arteries increases by 25–35% over the systolic-diastolic cardiac cycle [71, 72]. The elastic pulmonary arteries largely contribute to flow dampening, whereas more distal pulmonary muscular arteries/arterioles are stiffer, as seen in rabbits and dogs [73, 74] — although it is not clear in pigs [70] —, and regulate blood flow more actively through the constriction of the vascular wall smooth muscle cells [70]. However, it has been shown in guinea pigs that large pulmonary elastic arteries can also present a chemical- or stretch-induced strong myogenic response, enhanced in newborns [75]. Moreover, pulmonary (not systemic) arteriole smooth muscle cells are of particular importance in flow regulation induced by wall mechanics since they possess an oxygen tension sensor based on the redox equilibrium which triggers an increase in intracellular free calcium level resulting in smooth muscle cell — hence vessel — constriction when oxygen tension is low [69, 76, 77].

Finally, it has to be noticed that, besides the circumferential distension undergone by blood vessels under pressure, a limited extension with pressure also accounts for the mechanical properties of the arteries [78]. The longitudinal extension can be important in cannulated rat carotid arteries, up to 10–15% at a high pressure of 200 mmHg [79]. In vivo, elastic arteries also present physiological cyclic longitudinal extension, synchronised with circumferential extension during the cardiac cycle, in the range of only 4%, as demonstrated in the rat carotid artery and abdominal aorta [80]. This phenomenon, although limited because of a longitudinal elastic modulus markedly higher than the circumferential elastic modulus [80], probably contributes to a small part of the physiological elastic-reservoir function of elastic arteries. Moreover, longitudinal distensibility is strongly decreased in hypertension [79].

The mechanical properties of vertebrate arteries described above result from the structure of the arterial wall, constituted of wall cells interacting with several very specific arrangements of extracellular matrix proteins, including a highly resilient protein: elastin. The developmental appearance and structural organisation of these components in relation to function will be described in the following.

**LOWER AND HIGHER VERTEBRATES, MAMMALS: STRUCTURE–FUNCTION RELATIONSHIP IN THE MATURE ARTERIAL WALL**

In cross section, the vertebrate arterial wall is arranged in concentric zones, close to the organisation of the invertebrate and primitive vertebrate arterial wall: intima, media and adventitia [81]. The intima is mainly constituted of endothelial cells adhering to a basement membrane (luminal side), a few fibroblasts and smooth muscle cells, and sparse elastin fibres. A thicker internal elastic lamina separates the intima from the media. This elastic lamina is composed primarily of elastin fibres which account for the resistance to collapse of the vessel and global elasticity of the wall [23, 82]. Significant amounts of fibrous elastin, the highly resilient protein phylogenetically appearing only in vertebrates and not found in invertebrates or primitive vertebrates [12 – 15], and smooth muscle cells structurally arranged together into concentric elastic lamellae compose the major part of the media, while interspersed microfibrils and collagen fibres are also present. Collagen fibres, a few microfibrils and elastin fibres, as well as fibroblasts compose the adventitia [24]. Each one of these components account for part of the global behaviour of the artery.

Collagen fibres are rather unextensible, with a maximum extension in the range of 10% and an elastic modulus in the range of 1 GPa, at least several hundred fold higher than that of elastin fibres or smooth muscle cells. Aortic medial and adventitial collagen fibres are arranged into interspersed bundles with no definite spatial arrangement at low pressure (below 80 mmHg), and only medial fibres seem to really circumferentially align at higher pressure (100–150 mmHg) [24]. They mainly account for the stiffening of the vessel wall with increasing pressure at or above physiological blood pressure, therefore contributing to protection against damage or rupture [83]. When the arterial wall is chemically depleted from its collagen, the non-linear elastic property of the artery is lost, in particular the stiffness appearing above physiological blood pressure, with arterial diameter linearly increasing with pressure up to very high values [23, 24].

In resting conditions, the smooth muscle cells from both cannulated or in situ arteries do not seem to account for much of the elastic properties of the arteries. When these cells are not actively functional, for instance after poisoning by KCN application, they are highly distensible (up to 150%, elastic modulus in the range of 51 kPa) and the arterial distensibility curves as well as the circumferential elastic modulus are not or only slightly
modified (slight relaxation) in a wide range of pressure, including the physiological blood pressure range. This is true in both elastic and muscular arteries [50, 83–85]. In non-physiological situations, i.e. hypertension, simple smooth muscle cell proliferation of the vascular wall, leading to arterial wall thickening, seems to act positively by allowing a down-regulation of increased wall tension while preserving the mechanical properties of the arteries [86]. On the other hand, a major physiological role of smooth muscle cells is to regulate the vascular resistance and capacity, through their ability to decrease the luminal diameter and circumferential strain at physiological blood pressure when constricted, while constriction of these cells also decreases the arterial circumferential elastic modulus, i.e. increases distensibility, because of the diameter reduction and vessel wall thickening. This is also true in both elastic and muscular arteries [50, 84]. The endothelial cells at the interface between the blood and the wall are sensors which have an important role to play in the smooth muscle cell function since they produce and secrete a variety of molecules inducing constriction or relaxation of the smooth muscle cells, thereby initiating active vasoconstriction or vasodilatation.

Elastin is a resilient/rubber-like protein present in large amounts (elastin can account for more than 50% of the aorta dry weight) and arranged as a network of highly extensible fibres in the elastic artery wall. Elastin accounts for the arterial elasticity below and at physiological pressure [24]. The elastin fibre keeps its elastic properties up to extensions of about 140%, with an elastic modulus in the range of 0.4 MPa [26–28, 83]. The arterial wall media contains concentric elastic fibres made of 90% elastin and of microfibrils, the latter including aggregated fibrillin molecules and associated proteins. The elastic fibres developmentally arise from a smooth muscle cell-secreted microfibrillar scaffold (microfibril diameter of 10–12 nm) onto which smooth muscle cell-secreted elastin is deposited, aligned and cross-linked in a resilient fibrous network [29, 87–91]. Nevertheless, it has been reported in some exceptional cases that elastin containing elements can also be arranged in series with collagen fibres within the elastic lamellae, such as in the fin whale aorta [46]. In the general case, the elastic fibres are arranged in rather thick concentric and wavy layers called elastic lamellae, distributing the stressing forces uniformly through the media. Each concentric elastic lamella alternates with a physically connected concentric ring of smooth muscle cells to form lamellar units: a lamellar unit is composed of one elastic lamella plus one smooth muscle cell ring. With an elastic modulus of 0.5–0.7 MPa, a little above the elastic modulus of elastin alone (0.4 MPa) because of a slight contribution of the smooth muscle cells, the lamellar units seem to be the functionally resilient structure/unit of the arterial wall below and at physiological pressure, where they provide the artery with most of its flow damping properties [23, 24, 29, 83]. It is not surprising that the elastic fibre work is particularly efficient at and below physiological pressure, since the elastic artery major function is to compensate diastolic drop in pressure and maintain a minimal blood pressure, that is when cardiac blood pressure decreases to very small values.

The working arteries tend to distribute the global stress, imposed to the vessel wall by the specific conditions applying to a particular vessel (blood pressure, vessel radius), between all the lamellar units of the media which then share the global mechanical work. A single lamellar unit presents elastic properties allowing it to work within and to bear a certain range of mechanical load, which is best represented by the parameter called ‘tension’ (tension = intraluminal pressure × vessel radius). As a consequence, the number of lamellar units in the media of a particular artery have to be accurately adapted so that: (i) the tension per lamella is constant across species and perhaps across artery types; (ii) the global mechanical property of all the lamellar units taken together is appropriate to respond to the particular tension that the vessel bears. In mammals, the number of concentric lamellar units (therefore wall thickness) increases with arterial wall tension, i.e. with increasing blood pressure or/and vessel radius. This follows a very definite pattern so that the tension per lamella stays in the range of 1–3 N m⁻¹ [92]. This is true from the smallest mammals, such as the mouse (aortic diameter: 1 mm, number of lamellar units: 5, total wall tension: 8 N m⁻¹, tension per lamellar unit: ≈1.8 N m⁻³), to the intermediate-size animals, such as humans (aortic diameter: 18 mm, number of lamellar units: 60, total wall tension: 110 N m⁻¹, tension per lamellar unit: ≈1.5 N m⁻³), to the biggest ones, such as the fin whale (aortic arch diameter: 37 cm, number of lamellar units: 820, total wall tension: 2150 N m⁻¹, tension per lamellar unit: ≈2.6 N m⁻³) [46, 92]. Within the same species, the blood pressure and arterial radius decrease downstream the vascular tree while the arteries change from elastic type to muscular type, and it has been shown that, in rats, the number of lamellar units decreases accordingly from 10–13 in the ascending aorta, to 1–3 between the external iliac artery to the femoral artery, to no lamellar unit in smaller arteries, such as the deep circumflex iliac artery [93].

Despite an apparently clear structure-function relationship within the arterial wall, the particular role of certain components of the lamellar unit is still not elucidated. In particular, the mechanical role of microfibrils within the elastic lamellae remains unclear. The microfibril-based mechanics of the invertebrate and primitive vertebrate arteries lacking elastin, efficient under low pressure with elastic moduli of 0.01–0.15 MPa [10], suggests that microfibrils are unlikely to account for a significant part of elastic artery elasticity in highly pressurised systemic circulations with circumferential elastic moduli in the range of 0.5–0.9 MPa, such as in mammals (see above).
However, a recent work showed that chemically-produced specific removal of microfibrils from the elastic fibres of mature pig aortic tissue results in a significant 4–12% reduction of the modulus at low strain, and to a modulus increase at high strain [94]. These results suggest that microfibrils play a mechanical role in the systemic arterial wall, although their exact role is unclear: microfibrils could directly contribute to the global wall elasticity through their own mechanical properties, or they could play an intermediate role, transmitting the load from one elastic fibre to the other. These results also suggest that microfibrils could play an even more important role in elastic arteries from the lower vertebrates or the pulmonary circulation of higher vertebrates, in particular mammals.

These arteries undergo intraluminal pressures (10–30 mmHg) lower than in the systemic circulation and have circumferential elastic moduli in the range of 0.1–0.3 MPa, both close to those of invertebrate or primitive vertebrate arteries, and present a structural organisation similar to that of systemic arteries, including concentric elastic lamellae and collagen fibres [4, 70]. Therefore, it could be postulated that, in the elastic fibres of these arteries, microfibrils significantly share mechanical properties, i.e. the elastic work, with elastin in order to damp out the pressure fluctuation produced by the heart. This hypothesis is further supported by the structure-function relationship of the arterial wall in lower vertebrates, which suggests that the elastic lamellar unit is structurally and mechanically different from that of mammals. In the aorta wall of these animals (toad, lizard, snake), although the arrangement of the elastic lamellae is globally the same as in mammals (for instance rats), the lamellae are thinner (2–3 μm in place of 5–7 μm), more irregular and bear a tension per lamella of 0.3–0.5 N·m⁻¹, which is several fold lower than those of mammals [4, 92].

**LOWER AND HIGHER VERTEBRATES, MAMMALS: STRUCTURE-FUNCTION RELATIONSHIP IN THE DEVELOPING ARTERIAL WALL**

Because of the small size of organs in fetal and neonatal laboratory animals, relatively few mechanical studies have been performed on elastic arteries at these ages. Nevertheless, several studies have been performed in species of big size, mostly sheep, pig and humans, whereas many morphological studies of development have been conducted in the rat.

With the developmental stage, both in utero and after birth, the systemic blood pressure is regularly increasing while elastic arteries of the systemic circulation increase in diameter and wall thickness. For instance, in the sheep, whose gestation takes about 150 days, the blood pressure has been found near 20 mmHg at day 49 of gestation, 34 mmHg at day 101, 46 mmHg at day 120 and 76 mmHg at day 140 of gestation [95], whereas other reports describe values of 40 mmHg at 119 days of gestation, 56 mmHg in the 21 days old lamb and 68 mmHg in adults [48]. In the rat, the blood pressure steadily increases in the developing fetus from about 0 mmHg at day 10 of gestation, to 13–15 mmHg just before birth at day 21 [96], 35–40 mmHg after birth, reaching a final pressure range above 100 Hg one month after birth [97]. In humans, the systemic arterial blood pressure rises up to 22/15 mmHg (systolic/diastolic) in the umbilical artery at fourteen weeks of pregnancy, and, in foetuses close to birth, 74/62 mmHg in the umbilical artery [98], and 65 mmHg (systolic) in the left and right ventricles [99]. Immediately after birth, the systemic arterial blood pressure is in the range of 70/40 mmHg [100–102], and steadily continues to rise up to 120/80 mmHg in mature individuals (richard). On the contrary, the blood pressure in the pulmonary circulation decreases at birth from a fetal/neonatal pressure in the range of 50–65 mmHg in humans (26–45 mmHg in pigs), to 30 mmHg in humans after one day (23 mmHg at one day and 16 mmHg at one week in pigs) then to 15 mmHg after only three–four days (10 mmHg after two weeks in pigs), which is the pressure that will remain until adulthood [69, 70, 99].

The mechanical properties of the systemic arteries vary during development, with the progressively increasing blood pressure, and with the size and thickness of the vessels. The experiments performed in the carotid artery and the aorta of the developing sheep [48, 103], show that foetal (26 days before birth) or neonatal (21 days after birth) large elastic arteries are poorly distensible at low pressure as compared to adult vessels: the volume-per-unit length can increase by 30% between low intraluminal pressure and physiological pressure in foetal or neonatal arteries, whereas the increase is 80% in adult arteries in the same conditions. In the same time, the circumferential elastic modulus (stiffness) significantly increases (1.5–3 fold) from foetus to adults at the corresponding physiological blood pressures, and even more at high blood pressure. Interestingly, the circumferential elastic modulus at low strain-low pressure strongly increases between the foetal and neonatal stages (from 0.08 to 0.14–0.15 MPa), whereas it does not vary between the neonatal and the adult stages (0.14–0.15 MPa). However, the circumferential elastic modulus at high strain-high pressure does not vary between the foetal and neonatal stages (both 1.4 MPa), whereas it strongly increases between the neonatal and the adult stages (from 1.4 to 2.5 MPa). The increased stiffness is compensated for by the corresponding increase in blood pressure, vessel radius (therefore increased wall tension) and vessel thickness occurring in the same time and leading to higher arterial wall distension [48].

On the contrary, pig pulmonary arteries tend to become less distensible in the week following birth, from
a maximum of 3 fold down to 1.5 fold, while the blood pressure is rapidly decreasing and the wall is thinning. However, the circumferential elastic modulus, and the arterial diameter, of these arteries has been found to increase with the postnatal pulmonary artery remodelling in pigs, with values in the range of 0.08 MPa at birth, 0.25 MPa one week after birth, and then to decrease back to about 0.15 MPa in four months old animals. These two phenomena allow the maintenance of a proper function of the pulmonary arteries in dramatically different intraluminal pressures, necessitating a high distensibility before birth because the arteries have to work at high pressure, and permitting a lower total distensibility after birth since the physiological pressure drops [70].

These developmental changes in mechanical characteristics, both in systemic and pulmonary arteries, are explained and correlated in time with the different dramatic changes occurring in the remodelling vessel wall composition and structure during development, and particularly around birth. As shown in the rat (gestation in the range of three weeks), the prenatal forming elastic aorta is first endothelium-based, with sparse surrounding collagen (until day 12), with a rapidly increasing number concentric layers of mesenchymal cells/myoblasts then smooth muscle cells from day 13 (1–3 layers) to 20 (5–9 cell layers). The initially microfibril-based elastic fibres appear at day 13–14 in the inner layers of the media, before elastin is synthesised (elastogenesis) by smooth muscle cells, which probably concomitantly loose their contractile phenotype in presumptive elastic arteries (not in presumptive muscular arteries) as shown in the chick [104], and accumulates on the microfibril scaffold in the last third of gestation. The elastic fibres then increase in size and number (day 17–19), before the first real elastic laminae start forming at and after day 20 in a few inner layers. The sequence of events and the pattern of appearance of elastic fibres is similar in other species, such as in the sheep [105–108]. In successive microscopic cross-sections of the prenatal development of the rat aorta (day 13 to 20), the cell and collagen areas decrease slightly from 78 to 64% and from 0.5 to 0.3%, respectively, whereas elastin area increases from 0.03% (1.6% at day 17) to 6.4% [105]. During this period, elastin synthesis — and amount in the wall — has been shown to be an important regulator of smooth muscle cell proliferation and organisation [109]. In the following early postnatal maturation, collagen content (weight/total wall dry weight) steadily increases more slowly (2 fold by the first month and 3 fold by the fourth month) and, although the smooth muscle cells proliferate, the relative cell content of the wall (cellularity) decreases (from 45% at one week to 31% at 154 days). In the same time a rapid increase in elastin content (more than 5.5 fold in the first month, then reaching a plateau) and elastic fibre thickness, accounting for most of the early increase in wall thickness, takes place, while the wall tension increases several fold by the second month, and the number of lamellar units increases in parallel to the rising blood pressure [96, 97, 110–112].

In the sheep, although the aortic wall smooth muscle cells proliferate, the cellularity of the rapidly thickening wall (also) decreases with development: −46% between the 26th day before birth and the 21st day after birth, and an additional −43% between postnatal and adult sheep. Therefore, the neonatal wall thickening is mainly due to extracellular component synthesis, in particular elastin, leading to thicker elastic lamellae. The perinatal 89% increase in the low strain-low pressure circumferential elastic modulus (between the same fetal and postnatal stages) is correlated in a time-manner with the 69% perinatal increase in aortic relative elastin content, suggesting that the low strain-low pressure circumferential elastic modulus is closely associated with elastin. By comparison, the 88% increase in high strain-high pressure circumferential elastic modulus (between postnatal and adult stage) is poorly correlated with the 20% increase in relative collagen content from postnatal to adult animals, suggesting that the high strain-high pressure circumferential elastic modulus is associated with collagen content and the following collagen fibre cross-linking rather than with collagen content alone [48, 113]. In the wall of elastic arteries, decreased cellularity, rapid increase in elastin content before early plateau (after one month in the rat), and steady low collagen content increase in the perinatal period seems to be a general phenomenon, also seen in humans and rats [97, 110, 114].

**EFFECTS OF ALTERATIONS IN THE ELASTIC FIBRE COMPONENTS ON ARTERIAL STRUCTURE AND FUNCTION**

There are basically two causes for alteration of arterial elastic fibres, whose main components are elastin and microfibrils: a defect in its formation, because of genetic disease, or physiological or pathological degradation with age or vascular disease.

In the first case, the disorder could be caused by alteration in the elastin or the fibrillin genes. Human elastin is encoded by a single gene located on chromosome 7q11.23. It has been shown that alteration in expression of only one allele (hemizigosity), because of translocation, deletion or point-mutation, can result in the development of serious, potentially lethal, diseases: a vascular obstructive disorder of large elastic arteries called supravalvular aortic stenosis (SVAS) [115, 116], and a multifaceted developmental disorder including heart disease, hypertension and SVAS called Williams syndrome [117]. In a recently generated strain of mice hemizygous for elastin (ELN+/−), a potential animal model for SVAS, it has been shown that elasticity of the elastic arteries of these animals is altered, although the arteries maintain a normal diameter. Moreover, the number of elastic lamellae...
in the aorta wall of both SVAS patients and ELN+/− mice is increased by 2.5 fold and 1.35 fold, respectively, probably to maintain acceptable arterial elasticity and diameter [118, 119]. Alteration of microfibrils resulting from defects in the fibrillin genes do not result in obstructive vascular disease but rather in vascular dissection and degeneration, such as in the Marfan syndrome [30, 120].

On the other hand, elastic fibre degradation due to age (or disease) is caused by the action of elastases. This age-related phenomenon results in a decreased elastin/collagen ration, therefore an increased arterial stiffness, and leads to the presence of significant amount of degradation products (at least elastin peptides) in the tissues, and in the circulation where they can be found at concentrations ranging from 1 ng/mL to 10 µg/mL, depending on the reports [121−123]. A high affinity receptor of these elastin peptides is present on several cell types, including vascular endothelial and smooth muscle cells, leading to numerous biological activities. In the blood vessel wall, elastin peptides regulate enzyme and extracellular matrix protein synthesis and deposition (in particular elastin), cell attachment, migration and proliferation [124]. Elastin peptides also trigger aortic vasodilatation, through interactions with endothelial cells and smooth muscle cells [125−127]. The endothelium-dependent vasodilatation induced by elastin peptides is lowered with age and has been found to be mediated by endothelial production of NO resulting from activation of the endothelial membrane calcium channel leading to calcium influx and intracellular calcium rise [126, 128, 129].

CONCLUSION

The data provided by invertebrate as well as vertebrate models show that the flow dampening role of the large elastic arteries proximal to the heart has been conserved throughout evolution. This function is based on the non-linear elasticity of the arterial wall, a property which is provided by the presence of composite materials which allow high distensibility at low intraluminal pressure and lower distensibility at high pressure. Microfibrils seem to be responsible for both of these properties in the low-pressure circulation of some invertebrates and primitive vertebrates, whereas an interplay between elastin/elastic fibres, collagen and possibly microfibrils seem to play the same role in the arteries of lower and higher vertebrates, including mammals. Observations of the cardiovascular system evolution suggest that elastin, which first appeared in vertebrates, has been evolutionarily selected for because its mechanical properties are adapted to elasticity, therefore functionality, of elastic arteries working at higher blood pressure and bearing more important differences in pressure during the cardiac cycle. Moreover, developmental studies of mammalian circulatory systems and arteries show that there is a regular increase in blood pressure throughout the prenatal and postnatal period, and that microfibrils appear in the arterial wall before elastin, which generally appears only in the last third of gestation. These findings suggest that early synthesised wall microfibrils could provide the arteries with resilience in the early stages of cardiovascular development, possibly together with collagen, as long as the blood pressure stays below a threshold value. Beyond the threshold pressure, above which microfibrils would not be efficient alone, another resilient protein working at higher pressure would be needed in order to maintain the wall elasticity: elastin, and elastic fibres. Therefore, a mechanical continuum can be postulated during prenatal development, involving sequential synthesis of different resilient proteins effective in different pressure ranges. In that case, the regularly increasing blood pressure and resulting vascular wall cell stress could act as a trigger, sequentially turning on and off the genes of the resilient proteins involved. Further studies are needed to conclusively reject or confirm this hypothesis.

REFERENCES