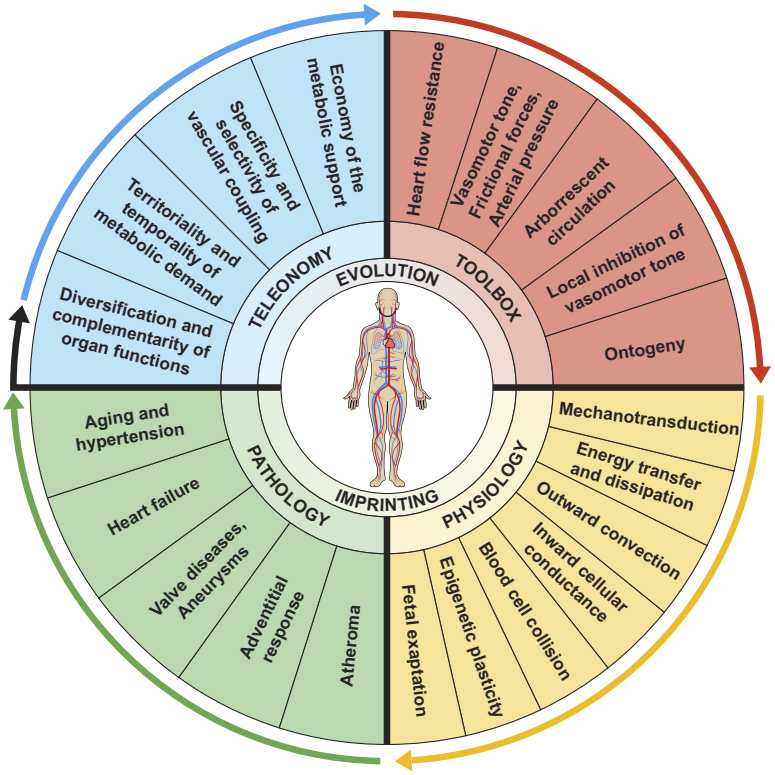
Physiological Reviews

Review Article

PHYLOGENIC DETERMINANTS OF CARDIOVASCULAR FRAILTY, FOCUS ON HEMODYNAMICS AND ARTERIAL SMOOTH MUSCLE CELLS

GRAPHICAL ABSTRACT



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KEYWORDS

arterial tone; energy dissipation; energy transfer; epigenetic; kinetic energy; local vasodilation; mechanotransduction; ontogenesis; potential energy

CLINICAL HIGHLIGHTS

- The "objective" of the circulatory system evolution is to accompany the global development of the increasingly complex animal's vital capacities, leading to humankind.
- The motor driving evolution of the circulation is to reach the most exact coupling between metabolic support (vascularization) and functional localization and activities of organs.
- Evolutive acquisition of arterial blood pressure is therefore a consequence of this teleonomy, but not its driving force.
- There are numerous physiological consequence of this evolution including mechanotransduction, mechanical energy transfer and dissipation, outward convection of plasma components, inward cellular conductance, blood cell collision, environment-driven smooth muscle cell phenotypes, exaptation and footprints on ontogeny...
- This evolutive adaptation is also the most common denominator of arterial disease, a predominant cause of death and disability.

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PHYLOGENIC DETERMINANTS OF CARDIOVASCULAR FRAILTY, FOCUS ON HEMODYNAMICS AND ARTERIAL SMOOTH MUSCLE CELLS

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Michel J-B. Phylogenic Determinants of Cardiovascular Frailty, Focus on Hemodynamics and Arterial Smooth Muscle Cells. *Physiol Rev* 100: 1779–1837, 2020. First published January 30, 2020; doi:10.1152/physrev.00022.2019.—The evolution of the circulatory system from invertebrates to mammals has involved the passage from an open system to a closed in-parallel system via a closed in-series system, accompanying the increasing complexity and efficiency of life's biological functions. The archaic heart enables pulsatile motion waves of hemolymph in invertebrates, and the in-series circulation in fish occurs with only an endothelium, whereas mural smooth muscle cells appear later. The present review focuses on evolution of the circulatory system. In particular, we address how and why this evolution took place from a closed, flowing, longitudinal conductance at low pressure to a flowing, highly pressurized and bifurcating arterial compartment. However, although arterial pressure was the latest acquired hemodynamic variable, the general teleonomy of the evolution of species is the differentiation of individual organ function, supported by specific fueling allowing and favoring partial metabolic autonomy. This was achieved via the establishment of an active contractile tone in resistance arteries, which permitted the regulation of blood supply to specific organ activities via its localized function-dependent inhibition (active vasodilation). The global resistance to viscous blood flow is the peripheral increase in frictional forces caused by the tonic change in arterial and arteriolar radius, which backscatter as systemic arterial blood pressure. Consequently, the arterial pressure gradient from circulating blood to the adventitial interstitium generates the unidirectional outward radial advective conductance of plasma solutes across the wall of conductance arteries. This hemodynamic evolution was accompanied by important changes in arterial wall structure, supported by smooth muscle cell functional plasticity, including contractility, matrix synthesis and proliferation, endocytosis and phagocytosis, etc. These adaptive phenotypic shifts are due to epigenetic regulation, mainly related to mechanotransduction. These paradigms actively participate in cardio-arterial pathologies such as atheroma, valve disease, heart failure, aneurysms, hypertension, and physiological aging.

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I. INTRODUCTION

In the beginning was the heart, and the heart generated pulsatile flow (kinetic energy), which became systolic/diastolic pressures (potential energy) and took residency among mammals.

Following the anatomical descriptions by Michel Servet (1511–1553) and Andreas Vesalius (1511–1553), William Harvey (1578–1657) described experimentally for the first time the physiology of the blood circulation in mammals. He applied venous and arterial ligatures in 1619 (work published 1628 in "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus," Anatomical exercises on the motion of the heart and blood in animals) and observed a highly pressurized arterial flow (ligature hard to tighten on conductance arteries) and a low-pressure venous flow (ligature easy to tighten on conductance veins), animated by the pulsatile heart beats (270). His observations also included that "the forward flow of blood impeded (by the tight) and its impact is reflected backward" (Exercitationes Duae Anatomicae De Circulatione Saguinis Ad Joannem Riolanumn filium. Rotterdam, 1649). Marcello Malpighi (1628–1694) completed this macroscopic description by making a microscopic observation of capillaries in the frog and then in mammals (572). Malpighi also suggested that nature achieved its great works in large animals after undertaking a series of attempts in lower animals. Since the 17th century, our anatomical and functional knowledge of the circulation has continuously increased, progressing to a more complete description of the evolution of the heart, vessels, and blood at the tissue, cell, and molecular levels from invertebrates to mammals, and in particular in humans.

In parallel, based on the observations of living systems throughout the world, the first theories of the evolution of species were put forward, particularly by Jean-Baptiste Lamarck (Philosophie zoologique, 1809), who proposed the inheritable transmission of phenotypic adaptations, driven by environmental constraints. This was followed in 1859 by Charles Darwin's principle of natural selection under environmental pressure (62, 184). These two observational analyses have led to continuing challenges in modern biology, with the Lamarck view being somehow resurrected by the discovery of the epigenetic modulation of gene expression (255) (neo-Lamarckism), in which the environmental constraints, including biophysical factors, drive the stochasticity of the evolution of the genome, and Darwin's view being rather restricted by the discovery of random genetic mutation (201, 570) (neo-Darwinism) (124, 289a, 369). Genetic enthusiasm, however, has been mitigated by the recent progress of genetic approaches in the numeric era. Heritability of epigenetic footprints has been analyzed in inter- and transgenerational inheritance (218). These evolutive paradigms were progressively developed from 60 yr ago, when Conrad H. Waddington (559) introduced in 1952 the notion of accelerated genetic assimilation (illustrated by the crossveinless gene in *Drosophila*), to today, through the concept of epigenetic memory or (re)programming (558). Nevertheless, the evolution of the circulation from fishes to mammals is a particularly rich integrative synthesis of these theories, involving mainly the acquisition of progressively increasing peripheral frictional forces (resistance to flow) due to the arterial smooth muscle cell (SMC) contractile tone, leading to highly pulsatile arterial blood pressure and its effects on the structure and function of the heart and wall tissue and its main stromal SMC component in conductance and muscular arteries.

The aim of this physiological review is not to provide an exhaustive description of the evolutionary molecular physiology of the circulation but to propose a holistic synthesis of how the teleonomy of evolution has determined the functional and structural biology (183) of the human circulation and how it impacts human pathologies in arteries and left ventricle (LV). The human circulation evolved from exaptation, natural selection, and epigenetic adaptation (430) via bidirectional crosstalk between hemodynamic forces and functional and structural plasticity of arterial structures. We will focus on the arterial SMC, which is the effector of peripheral resistance that determines arterial pressure, locally regulating blood flow, and is also the main mural cell to react to this pressure loading in mammals. More specifically, we will discuss how this adaptation impacts the specific human susceptibility to cardiovascular diseases (CVD), mainly concerning conductance arteries and the LV diseases in the context of time, from fetal life to aging.

II. PHYLOGENESIS OF THE CIRCULATION (FIGURE 1)

A. From Invertebrates to Vertebrates

The initial circulation in invertebrates is characterized by the appearance of an archaic beating pump as a myoepithelial tube capable of peristalsis initiated by motoneurons from neural ganglia (annelids). In mollusks, the heart has only two chambers, an atrium and a ventricle, separated by an archaic valve preventing backflow during ventricular contraction (502). In crustaceans, the circulation of hemolymph (a viscous liquid) is driven by a single contractile chamber (ventricle) ejecting to the gills through the sinus and regulated by motoneurons and interneurons. Due to the phasic nature of the heart's pumping ability, diastolic filling versus systolic ejection, the generated flow is pulsatile. This capacity to move interstitial hemolymph in an open vascular system increases the probability of interactions between energetic substrates, particularly phosphoryl transfers (307), and functioning tissues, enhancing their diversification. In crustaceans, the vessels are tubes limited by the basement membrane of neighboring tissue and a collagen basal lamina (486). These tubes are devoid of an endothelial lining, and the neurovegetative system mainly develops as parasympathetic cholinergic enteric nerves.

In invertebrates, hemolymph and hemocytes are respectively the soluble and cellular components of the moving

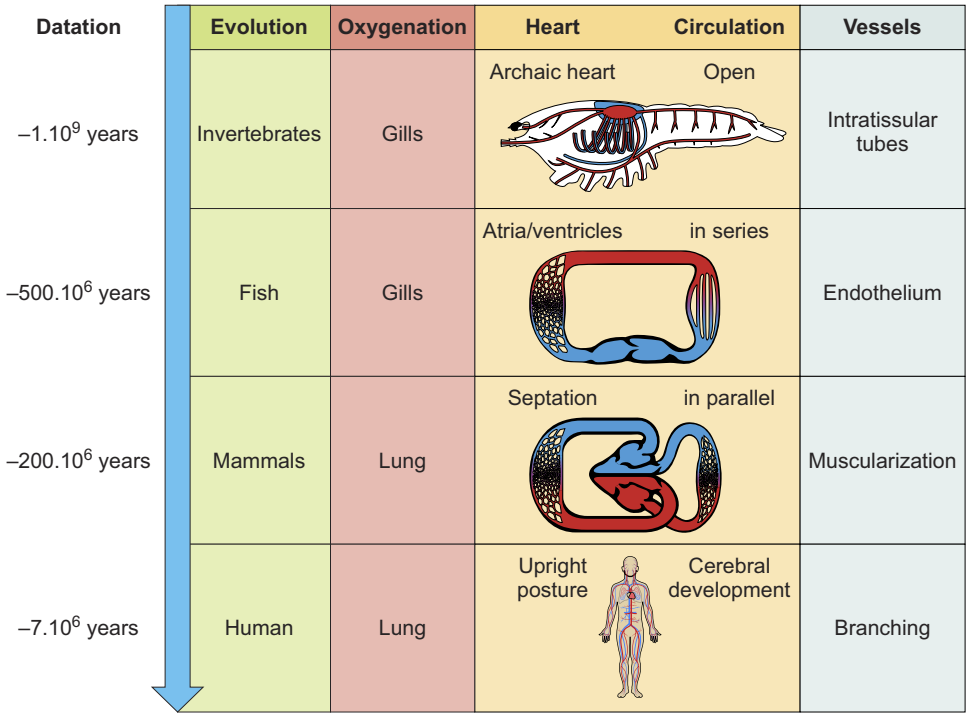

FIGURE 1. Evolution of the circulation accompanying the general evolution of species. The circulatory system progresses during the evolution of species from an open system, to a closed "in series" system in cold-blooded fish, and then to a closed "in parallel" warm-blooded one in mammals, including the highly pressurized arteries allowing specific local vasodilation, adapted to the metabolic demand of organ function, and finally, to a system permitting upright posture in man. [Lobster circulation image is from McMahon (337a), with permission from *Journal of Experimental Biology*. The mammal art is from John Farrelly (http://captainwonder.com/illustration/circsystem). Other clipart are from Docplayer (https://docplayer.info/) and Great Neck Public Schools (https://www.greatneck.k12.ny.us/) and used per their terms of use.]

extracellular fluid. Hemolymph and nucleated hemocytes (173) are directly involved in *1*) the coagulation system (93, 261), which is able to stop extracellular fluid loss; *2*) innate immunity (70), which is able to limit pathogen diffusion via encapsulation, nodulation, phagocytosis (2), and the release of bactericidal factors (70) and create immune memory via epigenetic footprints (188); and *3*) oxygen transport via intracellular (hemocyte) and extracellular (hemolymph) heme-related proteins (212, 531).

Therefore, various differentiated hemocytes and hemolymph proteins participate in the overlapping functions of coagulation, phagocytosis (261), innate immunity (259, 588), oxygen transport (106), and oxidation (566) in invertebrates. These poorly differentiated polyvalent cellular and molecular functions of blood in invertebrates have a direct impact on mammalian physiology and, by extrapolation, some human pathologies. For instance, among these functions, the ability of horseshoe crab hemocytes (amebocytes, water extract) to clot (coagulogen) in the presence of bacterial lipopolysaccharides (LPS) (innate immunity plus clotting) is used as a highly sensitive test, the Limulus-test (LAL-test), to detect bacterial endotoxins in numerous media (devices, therapeutic solutes) and biological fluids (253, 254).

In contrast, with the open circulation of invertebrates, an "in-series" closed circulation develops in lower vertebrates. In fishes (actinopterygians, teleosts), an abdominal heart, implanted on the deoxygenated (venous) side of the circulation, begins to become segmented with a sinus venosus, a filling chamber (atrium), an ejection chamber (a single ventricle), a bulbus arteriosus, and a conus arteriosus (outflow tract). The fraction of blood (a viscous liquid composed of plasma and circulating cells) ejected by the ventricle flows to the gills, where it is oxygenated by gas diffusion from water to blood through a capillary system. The oxygenated blood flows in the dorsal aorta towards functionally active tissues, which are oxygenated via a peripheral capillary system. Fishes are cold-blooded animals (poikilotherms) (498), possibly involving overwintering and dormancy. Their basic circulatory anatomy, an anteroventral heart and a dorsal aorta distributing to the main organs, is conserved throughout the evolution of species, including mammals. Vessel wall elastin exists in teleosts specifically in the ventral conus arteriosus, in which some resistances (mural cells tonic cytoskeleton) and elastin dampen the ventricular outflow, dissipating the cyclic kinetic energy (Ek) upstream to the gill capillaries (64, 243). In contrast, it appears that there is no elastin in fish aorta (114). Therefore, frictional viscous forces (resistance to flow) are lower in the dorsal circulation (oxygenated blood) as compared with the ventral part, and blood pressure is slightly higher in ventral than in dorsal vessels (see below: zebrafish). These observations underline the role of frictional forces to drag kinetic energy to protect the gill capillaries from the impact of the cardiac cyclic outflow. The closed circulatory vessels consist of endothelial tubes. Since the fish circulation is a closed system with marginal dissipation, the law of conservation of mechanical energy is approximatively applicable. The pumping activity of the heart muscle is sufficient to maintain Ek throughout the whole circulation in fish.

The autonomic nervous system develops in fish with both cholinergic parasympathetic nerves, mainly enteric and cardiac nerves (decreasing in heart rate), which predominate, and adrenergic sympathetic nerves of the opposite effects,

which progressively extend. This autonomic nervous control is mainly focused on heart rate and inotropy and on the gill circulation. Fishes can monitor external (water composition, external pressure, water temperature) and internal (feeding and metabolic elevation) environmental conditions via specific receptors, particularly those localized in the gills, which initiate cardiovascular control by the central nervous system. Nevertheless, teleosts are extremely diverse, and therefore the adaptation of the autonomic nervous system is variable, ranging from loss of control to fully developed control systems (reviewed in Ref. 470).

A specific coronary circulation appears during the evolution of fish. In a majority of teleosts, the myocardium is composed of spongy tissue (trabeculae) that is metabolically supplied from luminal venous blood (in 60% of fish species). However, some long traveling teleosts (Salmonidae, for instance) develop a more compacted myocardium, necessitating direct vascularization from the dorsal aorta, allowing oxygenated blood to supply the outer compact layer of the ventricular myocardium, whereas the luminal venous blood continues to metabolically support the inner spongy layer (146). Due to the myocardial contraction and the low perfusion pressure, retrograde flow can be observed in the coronary artery during systole (159). The myocardial contraction compresses the intramyocardial vessels, flushing blood into the coronary venous system but also into the coronary arteries. The development of a specific coronary circulation in long traveling fishes is an excellent example of the evolutionary adaptations of the circulation to the metabolic demands of organs and of the specificity of coronary hemodynamics (phasic diastolic flow). In this initial evolutionary step in vertebrates, the circulatory energy is essentially kinetic here.

In this evolutionary context, the zebrafish experimental model provides new opportunities for exploring circulatory function in fish, including the existence or absence of the relationship between the circulation and gene expression (521). The anatomy and function of circulation in zebrafish is similar to that described for teleost fishes. The zebrafish heart is characteristic of a fish heart with two atria, a unique ventricle, and a bulbus arteriosus and a conus arteriosus upstream of the ventral aorta, giving rise to the afferent branchial arteries supplying the gill capillaries. Despite its small size, the unique ventricle is composed of both a spongy (trabeculae) endocardial layer and a more compact epicardial layer, perfused by coronary arteries originating from the efferent branchial arteries (oxygenated blood). As in other teleosts, the blood pressure is low in zebrafish: 2.5 mmHg at peak systolic pressure in the unique ventricle. Due to the resistance and Ek dissipation in the gill arterioles, the blood pressure is always higher in the ventral aorta (2.15 mmHg at peak flow) than in the dorsal aorta (1.50 mmHg at peak flow) (238). Interestingly, elastin expression is limited to the skeletal cartilage, the bulbus arteriosus, the ventral aorta (344), and the swim bladder (427). There is no elastin expression in the dorsal aorta.

As in other teleosts, the zebrafish vessels mainly consist of endothelial tubes lined with an endothelial cell monolayer, which is supported by a basement membrane mainly composed of collagen and adhesive proteins (fibronectin). Ectodermic cells from the neural crest invade the primitive ventral heart tube. A first wave invades the wall of the heart chambers, and cells give rise to myocytes (25–30 h post fertilization), while cells of a second wave (3 days later) migrate along the aortic arch and wrap themselves around the endothelial tube of the ventral aorta, the conus and the bulbus arteriosus, forming the mural cells of the heart outflow tract (92) differentiating into SMCs. Therefore, there is no striated-to-smooth muscle phenotypic transition in the outflow tract of zebrafish (192) unlike in gastrovascular cavities and peristaltic hearts described in many invertebrates. Initial vasculogenesis of the dorsal aorta consists of angioblast migration from the ventral mesoderm and aggregate budding on the midline, rapidly evolving into flattened dorsal aortic tubes preceding venous tube formation. The formation of the dorsal aortic tubes is vascular endothelial growth factor (VEGF) dependent (136). Vasculogenesis is completed by sprouting angiogenesis (473). In this angiogenic context, VEGFs, bone morphogenic proteins (BMPs), semaphorins secreted by avascular tissues, chemokines, and interendothelial cell communications (cadherin, Notch) play a predominant role in the guidance of budding, sprouting, and hollowing out of new endothelial tubes. Finally, blood flow and shear stress induce endothelial cell differentiation and participate in induction of endothelial tube wrapping by mural cells (98).

The dorsal aorta also consists of an endothelial monolayer surrounded by dispersed mural cells, pericytes, and SMCs (575). Three main functional proteins of SMCs have been cloned in zebrafish: α-SMC actin (575), SM22-α (transgelin, associated with the smooth muscle contractile apparatus) (590), and SMC myosin (MYH11) (3). In this context, Ando et al. (11) and Stratman et al. (507) recently demonstrated that these mural cells (SMCs and pericytes) play a predominant role in the structure and function of the aortic wall. They observed the mesodermic origin of these cells, migrating from the sclerotome (somite) towards the dorsal aorta, wrapping around the endothelial tube. Platelet-derived growth factor (PDGF)-BB and receptor signaling mediate this phenomenon in a large part. Stratman et al. (507) also demonstrated the structural role of these mural cells, which are capable of promoting the assembly of vascular matrix (basement membrane) and of limiting the dorsal aortic diameter. An experimentally induced defect in mural cells of zebrafish leads to a larger aortic diameter and a more distensible wall (507). Whereas endothelial cells are able to synthesize and degrade the matrix collagen by proteases, mural cells synthesize antiproteases promoting the

integrity of the arterial wall. Mural cells also promote adrenergic sympathetic differentiation of external neurons in a PDGF-dependent manner (156).

B. Adaptation to the Terrestrial Way of Life (FIGURE 2)

The passage from aquatic to terrestrial life (107) was a great leap forward, necessitating the adaptation of the circulatory system to a drastic change in environmental conditions. This involved extensive differentiation of organ functions, such as in the lung and kidney, development of the skeleton, limbs with digits (9), regulation of the internal environment (460), and the transition from poikilothermy (ectothermy) to warm-bloodedness and finally to endothermic homeothermy (37°C), etc.

These multiple evolutionary transitions were also associated with the passage from oviparity to viviparity. This shift was associated with a change in internal temperature. Squamate reptiles (lizards and snakes) are unique models for studying the evolution from oviparity to viviparity (382). These numerous adaptations have also involved many evolutionary exaptations and dead-ends. The evolution of coelacanths, lungfishes, and tetrapods (sarcopterygians), possessing fleshy fins, to four-limbed vertebrates are examples of these exaptations, preceding and allowing terrestrial development. Some teleosts possess a dorsal swim (gas) bladder, allowing them to remain at their current water depth without energy consumption. Lungfish (103) (dipnoi) acquired the ability to breathe air by functionally developing lung alveoli from this gas bladder, concomitantly to gills (262).

In these evolutive stages, transitions from ectothermy to endothermy and from cold- to warm-blooded circulations take place through heterothermy, associated with increasing functional activities and biochemical energy dissipation, generating predominant endothermic heat production. This transition not only involves endothermy but also the regulation of body temperature constancy (homeothermy) (191). Warm endothermy and homeothermy (37°C) promote biochemical activities through thermal molecular motion that can be monitored by magnetic resonance imaging (MRI) (401). Enzymatic activities are highly sensitive to temperature. The relationship between warm body temperature and activity is exemplified by hibernation as an adaptive process to low (winter) external temperature in fishes (498) and some mammalian species. Body temperature drops below 10°C, associated with reduced metabolic activity and torpor (232, 545). Given its ability to decrease metabolic activity, hypothermia may be of therapeutic interest (232). One application of hypothermia is to use it for inducing heart arrest and myocardial and eventually cerebral protection, during cardiac surgery. Different molecular pathways are involved in hibernation: adenosine in the central nervous system (CNS), hibernation specific proteins (HPs) produced by the liver, cold-inducing RNA-binding protein (CIRP), *CLOCK* and *BMAL1* genes, etc. (232, 545).

The main evolutionary step for the circulatory system was to become an in-parallel closed system in mammals, in contrast to the in-series closed system in fishes. One of the main adaptive measures was an extensive tissue and molecular remodeling (120) of the heart (46), transiting through cardiac shunts, a regulated mixture of oxygen-rich and oxygen-poor blood, and finally a progressive septation of the heart chambers, involving first the septation of the atria, followed by the ventricles and the right and left large arteries in reptilians (224). The pulmonary versus peripheral resistances, under the respective controls of the cholinergic (parasympathetic, pulmonary) and adrenergic (sympathetic, peripheral arteries) systems, regulate the shunting proportions during this transition. The low oxygen partial pressure resulting from the mixing blood is compensated for by a sixfold increase in red blood cell (RBC) diameter (50 μm), compared with that of humans (7 μm) (214). Moreover, RBC diameter correlates with capillary diameter, minimizing the distance between RBCs and tissue, thus optimizing gas exchange (495). The oxygen transporting ability of hemoglobin is also modulated by globin isoform

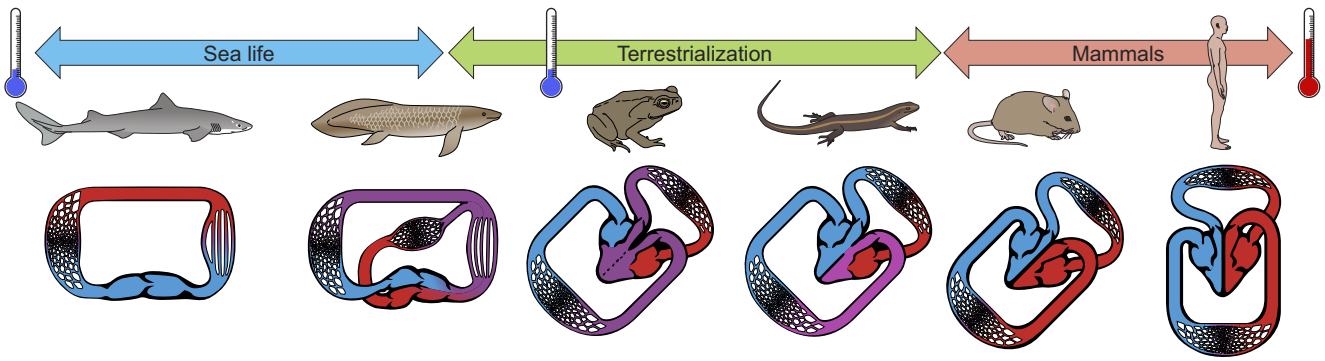

FIGURE 2. Terrestrialization was associated with important transitions in morphology and functions of all organs including the circulation.

expression, observed in phylogenesis and ontogenesis (506). This phylogenic heart septation event is recapitulated in the process of ontogenic septation, which takes place in the fetal heart in mammals and is mainly related to epigenetic involving three-dimensional chromatin remodeling processes (reviewed in Ref. 371).

Progressively, sympathetic innervation increased, whereas parasympathetic activity decreased, enhancing both the oxygen saturation and the frictional viscous forces in the arterial system, on one hand, and the specific venous characteristics (low oxygen saturation/low resistances) in the pulmonary artery, on the other hand. A low blood pressure and velocity in the pulmonary circulation is necessary to achieve maximal diffusion of gas through a very thin air-blood barrier. With the complete septation of the heart and arterial trunks in mammals and birds, the two systems became entirely separated and thus operate in parallel. Compared with amphibians (20–40 mmHg), arterial pressure progressively increases in reptilians (40–60 mmHg) to reach high values (120 mmHg) in mammals.

1. Gravitational forces

Among mammals, there is a huge pressure range in relation to specific environments and posture, including the highest value in the giraffe (>200 mmHg) in which the cardiac muscle weight reaches 2–3 kg (300–350 g in human). This is proportional to the body mass but limits cardiac output (heart rate 55 beats/min), as LV cavity is small, low stroke volume) (494). This compensates the high gravitational forces (negative work) due to the exceptional length of the neck (421).Functional and structural resistances in the leg arteries (increased muscularization) also compensate for this gravitational forces (428). When drinking, the giraffe lowers its head to the ground level (–4 m), and the arterial pressure acutely increases to 280–160 mmHg, but progressively normalize, whereas venous blood pools in the jugular veins associated with an important increase in venous pressure (from 0 to 45 mmHg) causing an important increase in jugular vein cross-sectional area (from collapse to 3 cm^2) (68). This neck tilt down is associated with autoregulation of pulsatile flow in arterioles (mechanical energy dissipation due to frictional forces) which compensates for large changes in arterial pressure (331). In humans (*Homo erectus*), the pressure stability associated with environmental changes during exercise (485), the change from supine to upright posture (gravity), and life in space (microgravity) (318) is mainly maintained by the baroreflex.

The evolutive progressive acquisition of arterial blood pressure is associated with the structural layering of the arterial wall from inside to outside, involving the muscularization of the media and the development of the adventitia. The adventitia, the outer loose connective tissue layer, conveys sympathetic nerves and a complete vascular system: arterioles, capillaries, veins (vasa vasorum), and lymphatics. The outer adventitia extends through the peri-arterial adipose tissue. Adventitial components inwardly signal to the media using intracellular signaling and intercellular conductance (see below). In contrast, the medial muscularization evolves without specific tissue angiogenesis, remaining an avascular tissue (except the external 1/3 of the thoracic aorta) (583) and therefore represents an immune privileged site, poorly accessible to leukocytes in the absence of intramural capillaries and venules (357). Physiologically, the media are directly fueled by outward convection-diffusion of oxygen from circulating RBCs into the plasma and then radially into the arterial wall interstitium and cells (see below). Similarly, glucose is outwardly convected from plasma into the wall. The endothelium remains a monocellular layer as in fish.

Kidney function develops in parallel, regulating the interior fluid environment evolving with terrestrialization. In this context, the renin endocrine system appears as a link between the homeostatic function of the kidney and the circulation, able to respond differently to acute or chronic stimuli by using SMC plasticity. Renin first appears in teleosts (396), but its functional complexity greatly increases during the transition from aquatic to terrestrial life, participating in terrestrial adaptation, which involves numerous functions linking the kidney to internal homeostasis, arterial blood pressure, salt retention, hormonal stimulation, endocrine and local systems, etc. In this context, the epigenetic memory of renin secretion and myoepithelioid phenotype recruitment (hyperplasia) of SMCs in afferent arterioles to glomeruli were recently deciphered (326). The renin gene is a very old gene (400×10^6 years), and cells expressing renin predate SMCs in the glomerular afferent arterioles (480). In quiescent conditions, SMCs in the glomerular arterioles are of a canonical phenotype (α-actin, myosin), and renin-secreting myoepithelioid cells are rare. However, environmental chronic stimulating conditions (decrease in blood pressure, β-adrenergic stimulation, loss of sodium, inhibition of angiotensin II feedback, etc.) cause an increase in renin secretion via hyperplasia of myoepithelioid cells. The upstream adjacent arteriolar SMCs shift their phenotype to a myoepithelioid one (348). This ability both to conserve the smooth muscle phenotype and to reacquire the ability to synthesize and secrete renin are under epigenetic memory control. A super-enhancer locus [topologically associating domain, TAD (13)], functionally involving lysine 27 acetylation of histone H3 (H3K27) and chromatin recruitment of p300 as histone acetyltransferase (HAT), controls the expression of numerous transcription factors and pathways, including the cAMP signaling and Notch pathways, which re-enable the switch to the myoepithelioid phenotype of arteriolar SMCs and renin secretion (326). These data provide evidence of the importance of chromatin three-dimensional remodeling in the definition and plasticity of the SMC phenotype. The epigenetic molecular memory and the ability of these signals to diffuse from one SMC

to the next via connexins (see below) induce hyperplasia of the juxtaglomerular apparatus in response to chronic stimuli of renin synthesis and secretion, including low perfusion pressure.

C. Evolutive Ontogeny

As described above for terrestrialization, the change in reproductive mode from oviparity to viviparity was also an important step in evolution, linked in part to the change in internal temperature. Oviparity is characterized by the formation of eggs, containing the embryo and a yolk sac, covered by a more or less calcium-rich shell, which are retained within the body for most of the embryonic period. In the second phase, the egg is laid, and the embryo matures externally (incubation period) depending on its own energetic yolk reserve (lecithotrophy). Since the yolk sac is relatively easy to observe, the initial descriptions of vasculogenesis and angiogenesis were made from bird eggs more than 100 years ago (534). Observation of the initial vascular development showed the formation of a capillary plexus at the surface of the yolk sac, which in part regresses in relation to the blood flow that selects the larger endothelial tubes. These develop and grow as the vitelline artery in relation to the embryo and the pulsatile embryonic heart, i.e., the venous return, ultimately forming a closed system. These observations have been progressively enriched with new information concerning the evolution of the capillary plexus to a branching and enlarged organized system through a pattern of capillary selection and increased blood flow rate (231). Finally, this evolutionary selection was described as an arterial pole and a venous pole, and mechanisms of disconnection of the arterial capillaries and reconnection to the venous pole are supported by endothelial cell plasticity in response to flow (frictional forces) generated by the beating heart (300).

In contrast to oviparity, viviparity retains the embryos in utero throughout the embryonic and fetal phases. In this reproductive strategy, the energetic support of development comes directly from the nutrient and oxygen exchanges between the uterine circulation and the fetal placenta (placentotrophy) and represents an important step in evolution. The evolutive advantage of viviparity is the placenta's dynamic ability to adapt metabolic support to developmental demand (382) and therefore reversal from viviparity to the ancestral oviparity is extremely rare in evolution (190). For instance, both reproductive modes are present in squamate reptiles, sometimes from the same lineage (*Lacerta vivipara*) (513), and cold external temperature seems to be the environmental condition that promotes evolution towards viviparity. In oviparous squamate reptiles, the initial ovum is composed of the embryo and a large yolk sac surrounded by different membranes, including the outer eggshell. Squamates differ from birds in the cell components of the yolk sac and in the processes of vasculogenesis and angiogenesis associated with membrane dynamics (503). In particular, endodermic cells invade the yolk sac, and these cells are able to engulf the yolk by endocytosis and transport it towards the developing vascular system. The transition from oviparity to viviparity is ensured by prolonging intrauterine egg retention and by a considerable reduction in eggshell thickness, allowing the extraembryonic membranes and the uterine epithelium to be brought together to form a placenta. This evolution correlates with the decreased secretion of proteins and mineral components necessary for eggshell formation by the uterine gland (65). In this context, in all amniotes the yolk organ in oviparity may be considered a potential evolutive exaptation towards the formation of the feto-placental unit in viviparity. In particular, the "yolk placentae" in some reptilians develops as an intimate relationship between the embryo and the mother. A vascular splanchnopleure develops at the perimeter of the yolk sac. This yolk vascular system makes contact with the uterus if viviparity evolves and forms the umbilical cord. The vessels at the perimeter of the yolk sac directly participate in placentation in live-bearing lizards and snakes.

The development of the circulation in mammals is termed vasculogenesis in the embryo but angiogenesis in the fetus. Heartbeats appear first at 22 days of human gestation, and blood islands, composed of hemangioblasts derived from both the lateral mesoderm and the yolk sac (154), lead to the formation of angioblasts, endothelial cells, and hematopoietic cells. The heart beats generated pulsatile flow. Several growth factors [fibroblast growth factor (FGF)-2, PDGF-BB, VEGF] and frictional forces-dependent stimulation (483) control the angiogenesis. Extension of the vascular plexus takes place via sprouting and intussusceptive (splitting angiogenesis) growth, forming endothelial tubes related to VEGF receptor expression. Development of the fetal circulation is predominantly linked to placental function (153). Endocrine gland (EG)-VEGF (prokineticin, PROK1/2) plays a pivotal role in the specific development of placental angiogenesis and chorionic villi (7). Exchanges of oxygen, nutrients, and CO_2 between the mother to the fetus take place via interaction of the uteroplacental circulation (uterine arteries, decidual spiral arteries, intervillous spaces) with the fetoplacental circulation (umbilical arteries, fetal capillaries, umbilical veins). Oxygenated blood and nutrients are transported to the fetus by the single umbilical vein and conversely more mixed blood and fetal metabolic products are transported back to uteroplacental vein by the umbilical arteries **(FIGURE 3)**. There are some shunts (25% of arterial blood) within the placenta between the umbilical arteries and vein, adding kinetic energy in the umbilical vein.

Mesenchymal stem cells (MSCs) differentiate into mesenchymo-angioblasts, spread and adhere to fibronectin, and generate mural cells, SMC, pericytes, and bone marrow SMCs under FGF2 and PDGF control (493). Endothelial

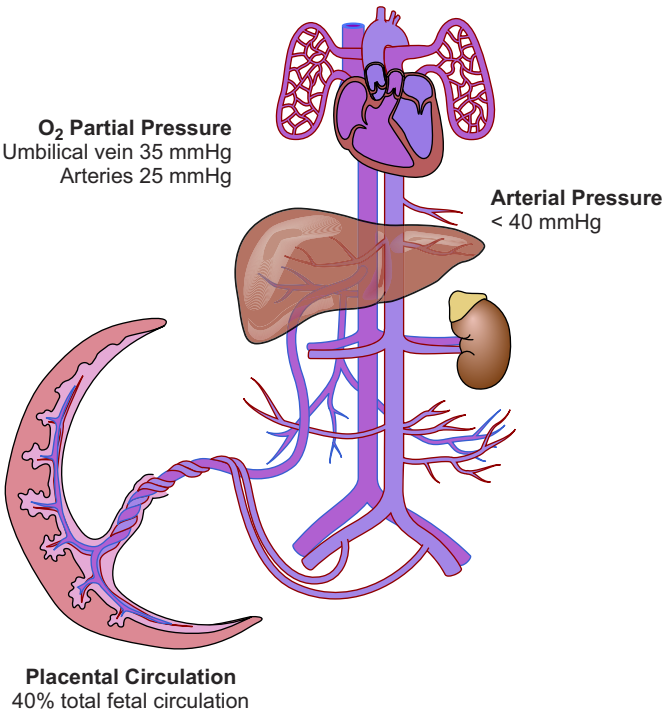

FIGURE 3. Circulation during fetal life in humans. The fetal circulation is complex, associating the fetus' own circulation to the placental circulation (viviparity). The fetal circulation is characterized by the absence of lung function, predominance of kinetic energy (flow), low arterial pressure, low O_2 partial pressure (relative hypoxia), and right-left shunts. The umbilical cord, involving the vein, the two arteries, and the placenta, is an integral part of the fetal circulation.

cells and SMCs are derived from the mesoderm, except for SMCs of the ascending aorta and corneal endothelial cells, which come from the neural crest (397) and SMCs of the coronary artery which originate from the epicardium and the neural crest as valvular interstitial cells (364). The orientation of human embryonic totipotent stem cells (hESCs) is sensitive to mechanotransduction; on one hand, culture of hESCs on a stiff or elastic scaffold orientates them towards mesodermal lineages, whereas their culture on soft substrates orientates them towards neural ectoderm (137, 425). On the other hand, culture substrate stiffness can regulate the YAP/TAZ signaling pathway (nuclear translocation) within the cell (113) (see sect. III*H*). ATP-dependent chromatin remodelers, DNA methyltransferase (DNMT), and HAT (p300) also play important roles in the progression of vascular cell differentiation from the neural crest (398) or the mesoderm (584). Nevertheless, the impact of these different origins on the ability of SMCs to adapt their phenotypes to environmental changes has not yet been explored in detail. It is also of interest to raise the question of the regulation of gene expression in cells of different embryonic origin towards the common pathway of the mature SMC phenotype. As in other organs, arterial architecture during the different stages of development is under the control of epigenetic regulation of gene expression (252). Besides flow-induced mechanotransduction, arteriogenesis is under the control of VEGFR2, at least in part, in a ligand-independent manner (extensively reviewed and illustrated in Ref. 490).

The partial pressure of oxygen in the umbilical vein and arteries is ~30 mmHg (3.9 kPa), and the fetal hemoglobin isoform has a higher affinity for oxygen than the adult isoform, binding oxygen from the maternal arterial blood more avidly (242). The relatively low O_2 partial pressure plays a role in inducing the expression of hypoxia inducible factor and VEGF during fetal life. The umbilical vein distributes blood to the inferior vena cava (ductus venosus), the liver, and the portal vein. Due to the exclusion of the lung parenchyma during fetal life, the blood flows from the right to the left atrium through the patent foramen ovale and from the right ventricle and pulmonary artery to the aorta through the ductus arteriosus. Positive pressure gradients from the right to the left atrium and from the pulmonary artery to the aorta are necessary for these shortcut circuits. The left ventricle pumps blood to the aorta, the brain, and then to the body and placenta. One part of the aortic and iliac arterial blood flow is diverted towards the bilateral (symmetrical) umbilical arteries. Functionally, the embryonic heart not only supports the pulsatile blood flow for the embryonic body but also the vital energetic support through the placental circulation. The fetal circulation is functionally described as a "via sinistra," which preferentially drives the oxygenated blood of the umbilical vein toward the right atrium via the ductus venosus (25%), and the foramen ovale. Left ventricular pumping ejects blood in the ascending aorta and the cerebral arterial circulation. In the "via dextra," the venous blood from the fetal body returns to the right atrium, right ventricle, and pulmonary artery and is propelled through the ductus arteriosus in the descending aorta and, at least in part, to the umbilical arteries and placenta. Everywhere in the fetal circulation the oxygenated blood is more or less mingled with deoxygenated blood, explaining the low O_2 partial pressure (67) **(FIGURE 3)**. Therefore, we can propose that the fetal circulation is a footprint of the intermediate mixed circulations observed in amphibian and reptile during the evolution of species.

Since the fetal heart beats, flow in fetal circulation is pulsatile; this pulsatility can be analyzed by Doppler ultrasound at different sites, including the placenta, the umbilical cord (pulsatile flow in umbilical arteries, continuous flow in umbilical vein), the fetal arteries (cerebral artery for the brain, descending aorta, shunts, etc.). The pulsatile velocity signal is composed of a systolic peak of velocity and a diastolic run on. These waveforms provide some relative calculated indices: pulsatility index, relative resistances, absent or reversed end-diastolic blood flow, etc. For the last 30 yr (323), these placental and fetal flow pulsatility indices have been used as prognostic markers of intrauterine fetal growth restriction. In healthy conditions, the placenta resistance is very low. In cases of impaired placentation, the uterine part of the pla-

centa is defective creating an increased impedance to flow, inducing an increase in umbilical artery pulsatility index or an absent or reverse diastolic flow (322). This increase in placenta impedance could be due to intervillus/intravillus structural and functional mismatch (475) leading to relative fetal hypoxemia. A decrease in pulsatile index in the middle cerebral artery (increase in diastolic run-on) associated with diastolic backflow in the aortic isthmus provides evidence of flow redistribution towards the brain (322). These different vascular changes associated with impaired placentation also impede the fetal growth and development. In the same way, pulsatility changes in the ductus venosus (diastolic backflow) can indicate a risk of cardiac insufficiency. These fetal anomalies can have postnatal consequences that persist throughout life (cardiovascular diseases, metabolic syndrome, hypertension) as developmental origins of diseases (203, 204). These developmental footprints on disease are essentially epigenetic by nature (554).

The blood in the fetal aorta is ~30–40 mmHg at the end of gestation. The fetal mixing circulation is essentially flow without important peripheral resistance (pressure), as in fishes. This fetal impact of flow on arterial structure is exemplified by the asymmetrical development of iliac arteries in cases of a single umbilical artery (343). In these cases, only one umbilical artery develops from one embryonic iliac artery, leading to an asymmetrical flow between the two fetal iliac arteries. As a consequence, the iliac artery supporting the umbilical artery and the homolateral leg flow develops more than the contralateral iliac artery supporting only the fetal leg flow. At the end of gestation and after birth, the homolateral iliac artery is larger than the contralateral one, and its wall is thicker and richer in elastin and in other extracellular matrix (ECM) components (conductance artery). In contrast, the smaller contralateral iliac artery appears hypoplastic, resembling a muscular rather than a conductance artery (343). In this context, a single umbilical artery, either associated with other congenital or chromosomal anomalies or isolated, represents a risk factor for poor perinatal outcome (383). Since the totality of blood volume (body + placenta) flows through the aorta during fetal life, this could explain why the aortic diameter is so large, forming an elastin-rich arterial blood reservoir after birth. Consequently, the shear stress is low (5–8 dyne/cm^2), whereas the tensile stress is high in relation to the large diameter (Laplace law) of the aorta after birth. These observations also provide evidence for the role of shear stress (frictional forces) as the driving force for fetal structural exaptation (preprograming) of the arterial wall, in the absence of high arterial pressure. Of note, the fetus is warm-blooded but essentially exotherm, and its temperature depends on the mother's temperature through amniotic fluid.

At birth, circulatory arrest in the denervated umbilical cord mediated by powerful vasoconstriction of the umbilical arteries and vein, followed by first breath inflation of the lung, induces an increase in body blood flow (loss of resistance), with a decrease in pressure in the pulmonary circulation (376). Conversely, the increase in arterial pressure is due to an acute rise in arterial resistance. The initiation of the pulmonary circulation increases left atrial pressure, rapidly closing the foramen ovale associated with the gradual closing of the ductus arteriosus in response to vasoconstrictive prostaglandins of lung origin (226). Likewise, the peripheral frictional force rapidly rises in left side of the circulation in response to the catecholamine rush and SMC tonic contraction, under control of the CNS (411). Therefore, birth induces a complete change in hemodynamic load, involving not only flow as in fetal life but also arterial pressure and loss of umbilical flow. The adaptation of the wall to the pressure load is not instantaneous but is a progressive process, which takes place during the 16 yr of growth in humans from infancy through childhood up until the end of puberty. For instance, the postnatal systolic and diastolic arterial pressures are 75/40 mmHg, respectively, 90/50 mmHg at 1 mo, 105/63 mmHg at 2 mo, and 106/69 mmHg at 1 yr (236) with the acquisition of upright posture. It is of interest that the progressive increase in arterial pressure from childhood to adulthood is highly dependent on individual height (independent parameter) in the upright posture during growth (99), providing evidence for the role of gravitational forces in blood pressure development in humans (see above). Therefore, each evolutionary stage imprints the circulatory development in the fetus: early heartbeats, predominance of flow, intracardial shunts, and low arterial pressure. The transition from oviparity to viviparity thus introduces an entirely transient event, energetically and dynamically fueled by placental function (84). This allows for the development of organ function by an adapted energetic support. However, the birth revolution is not the end point, and the immature circulation continues to evolve throughout growth to adapt to the pressure load in the arteries, to gravity due to upright posture, to the increase in specifications and activities of organs, to terminate angiogenesis, etc., and finally to dynamically and permanently equilibrate the energy transfer and dissipation between flow and pressure dependent on mechanotransduction in matrix-rich conductance arteries, and on SMC connections in resistance arteries.

The acquisition of upright posture in *Homo erectus* (–2 × 10^6 yr) was associated with the sphenoid verticalization and the development of consciousness in *Homo sapiens* (–300 × 10^3 yr) and its translation by speech and writing, necessitating autoregulation of the cerebral blood supply, influenced by gravitational forces (50), vasomotor reactivity, and exact neurovascular coupling of cerebral blood flow to neuronal activities (580). The specification of cerebral blood flow is influenced by intracranial pressure (112) and

pulsatility of the cerebrospinal fluid (112), low cerebral resistance, and compliance of cerebral conductance arteries (536).

III. STRUCTURE/FUNCTION RELATIONSHIP WITHIN THE MAMMALIAN ARTERIAL CIRCULATION (FIGURE 4)

As described above, the main characteristic of the circulation in mammals is the in-parallel development of a low-pressure compartment involving the venous return and the pulmonary circulation and a highly pressurized arterial compartment, related to peripheral resistance to flow, involving complete heart septation.

The pulmonary circulation is a low resistance system with high pulsatile flow, comparable to the circulation in fish. Thus pulmonary circulation in mammals can be considered as an imprint of the "in series" closed circulation observed in lower vertebrate. The pulmonary compartment is essentially capacitive: changes in pressure are associated with changes in vessel diameter, and increased gas exchange capacity is associated with recruitment of new alveolar capillaries (591). In the pulmonary artery, the kinetic energy predominates and the pressure variations are directly dependent on flow and frictional forces on the wall and within the blood. Adaptation to exercise is a good example of this low resistive regulation (see Ref. 389 for complete review) in which exercise induced an important increase in pulmonary mean arterial pressure, from 15 mmHg at rest to 35 mmHg during exercise. This is particularly true in racehorses in which the mean pulmonary arterial pressure can reach 60–80 mmHg with a proportional increase in capillary pressure, at the height of effort. These observations are not without consequences, since they are associated with frequent pulmonary hemorrhages in racehorses (225). Such pathological hemorrhages are rarer in humans (122) but can reveal subjacent lung disease (pulmonary amylosis, pulmonary vein stenosis). Moreover, an exercise test could be used to predict chronic pulmonary hypertension (PH) (390). In this context, abnormal degradation of von Willebrand factor (vWF) is of prognosis value in PH (313) (see sect. VIC for more details on vWF and shear stress). The relationship between shear-dependent vWF degradation and pulmonary hemorrhages in this context remains to be established.

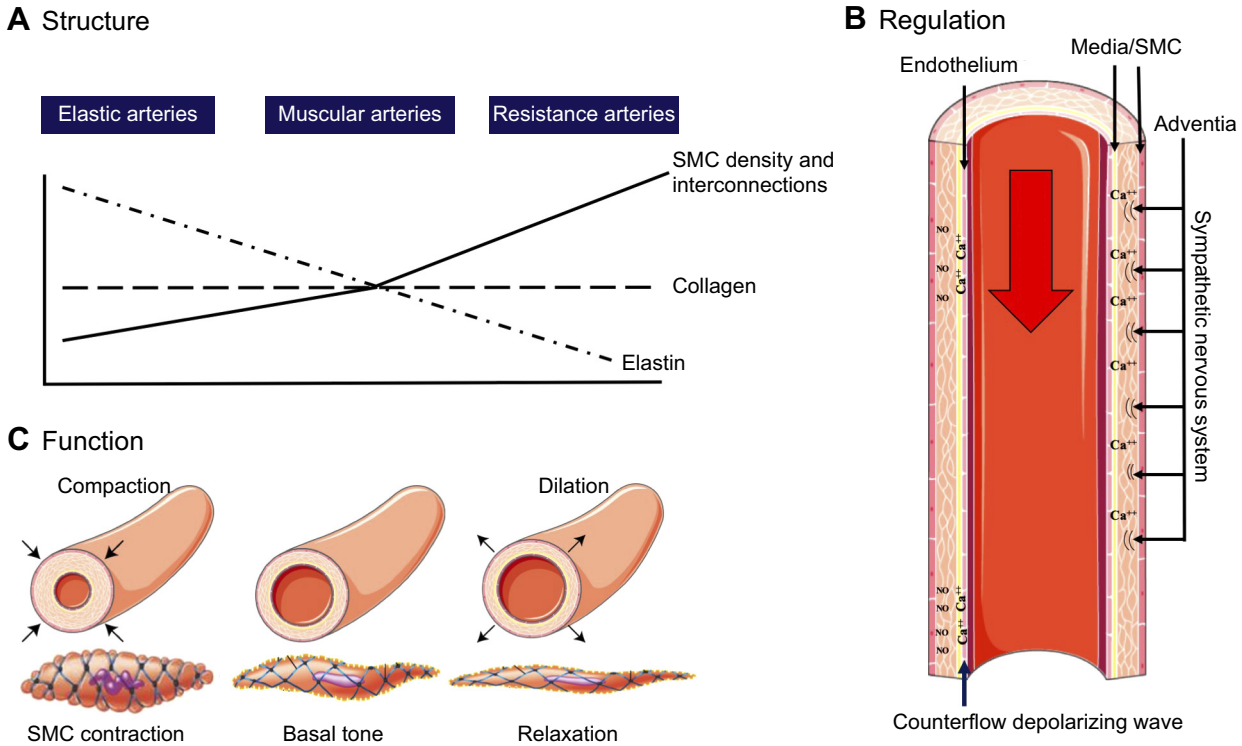

FIGURE 4. Structures/functions of arteries. *A*: the structure of arteries is dependent on their principal function: conductance and energy transfer for elastic arteries, local adaptation of flow to energetic demands for muscular arteries, high frictional forces, and mechanical energies dissipation for resistance arteries. *B*: contraction and relaxation of smooth muscle cells (SMCs) and their respective effects on compaction and dilation of the arterial wall tissue. *C*: regulation of vasomotricity involving maintenance of the arterial contractile tone by the adventitial sympathetic signals, which diffuse inwards via the medial SMC connexins; and the predominant role of endothelium in vasodilation via the flow-dependent shear stress and retrograde endothelial depolarizing wave, initiated by organ function and its upstream diffusion through the endothelial cell connections.

The mammalian heart functional architecture was poorly understood until recently. Francisco Torrent-Guasp in Spain described for the first time (1972) the ventricular myocardial band (for exact figures, see Refs. 64 and 537) between the aortic valve and the pulmonary artery orifice, which curls on itself in two (basal and apical) spirals, figuring an 8, clockwise dynamic loops and circumferential fibers, inducing contracting and twisting of the ventricular cavities. This functional architecture allows alignment of the LV cavity on the aortic orifice in isovolumic protosystole (elongation of the LV apex, and tubularization of the LV outflow tract) and during systolic ejection, with a minimum dissipation of velocity vectors. This model not only explains the systolic pre- and ejection phase, but also the diastolic phase of blood suction within the ventricular cavities, inducing vortices during LV diastolic filling (71) and the preorientation of this vortex towards the aortic root for ejection. The vortex corresponds to rotational kinetic energy without efficient translational motion. Diastolic vortices are inherent to the cyclic nature of ventricular function, including the velocities fillings of the LV cavity during diastole without outflow. In this evolutionary context, the pumping ability of the left ventricle is no longer just to generate phasic flow, as in fishes, but to generate phasic flow against the arterial peripheral impedances, generating arterial flow and pressure.

This functional anatomy also explains the specific phasic hemodynamics of the coronary circulation in the left ventricular myocardium. The contractile twisting force first completely impedes intramyocardial flow entry during systole but induces a highly pressurized blood stagnation in the epicardial coronary arteries, not compressed by the myocardial contraction. Second, systolic contraction squeezes out the intramyocardial diastolic blood volume into the venous sinus, causing venous flow ejection in the non-postloaded right atrium (94). Conversely, myocardial inflow in diastole is high, inducing a high frictional shear rate in coronary arteries.

Contrasting with the capacitive part of the circulation, the SMCs and ECM-rich walls of the conductance and muscular arteries support a basic and phasic tensional stress, proportional to the pressure and the vessel dimensions (Laplace law). The acquisition of SMC-dependent peripheral resistance in the distal compartment and high tensional stress in the conductance compartment made necessary the development of a topological arrangement of the arterial wall to enable it to assume these different functions **(FIGURE 4*A*)**. This differential topology also influences the mechanical transduction signaling in these two different compartments involving the predominant role for cell adhesion to ECM in conductance arteries (lower SMC density/high tensile stress), and for the intercellular connections in muscular and resistance arteries (higher SMC density/lower tensile stress) (see sect. III*G*). This involves a three-layered architecture comprising, from inside to outside, an endothelial monolayer already existing in the "in series" circulation in fish, a structurally intermediate media, variably enriched in SMC and ECM, and an external adventitia.

The "in parallel" implementation of the arterial system is associated with numerous bifurcations and branching arborescent structures, allowing a specific anatomical supply of oxygenated blood to functional organ-specific areas. Thus the arterial system is also longitudinally compartmented between conductance elastic and muscular arteries and more distal resistance arteries, including the intraparenchymal arterioles, flowing into the low-velocity and low pressurized capillary system. This implies mechanical energy (velocity and pressure) dissipation upstream to the capillaries. Both conductance and resistance arteries are composed of SMCs and ECM in different proportions. The mural cells present in fish evolve towards SMCs, enriched by a contractile apparatus that is able to maintain a functional mechanical tone via continuous activation by the sympathetic adrenergic tone. This tone maintenance is consumptive of biochemical energetic substrates (ATP and GTP). This is related to the presence within the SMCs of an actin cytoskeleton and smooth muscle myosin, sliding on actin, forming actomyosin complexes. This isoform (MYH11) is the most recently acquired contractile protein in vascular SMCs and the first to disappear in cases of SMC dedifferentiation (27). This isoform is physiologically and biochemically quite different from the sarcomeric cardiac and skeletal muscular myosins. The acto-myosin sliding in SMCs is more than 100-fold slower than in sarcomeric organization, and smooth muscle myosin interacts with other different proteins, such as caldesmon and calponin which are not present in the sarcomere (515).

Elastic arteries are richer than muscular arteries in elastin and collagen networks synthesized by SMCs, the main mesenchymal cells of the wall, but in these arteries, SMCs still conserve their contractile function through actomyosin sliding. In conductance arteries, the viscous dissipation of mechanical energy is represented by the dissipation of pressure and nonlaminar velocity vectors within the arterial wall (see sect. V*B*), whereas the frictional forces due to the longitudinal flow induce proximal reflective pressure waves, depending on the rigidity of the arterial wall and bifurcations. In contrast, wall elasticity and compliance in response to pulse pressure dampen the systolic arterial pressure and restitute (resilience) it as diastolic run-on flow in conductance arteries (mainly aorta) (240). The structure of the aorta wall is lamellar associating elastin with SMCs functions, and the number of medial lamellar units (wall thickness) is proportional to the dimension of the artery, whereas blood pressure is relatively constant throughout all mammalian species. This adaptation tends to maintain a constant tensile stress per lamellar unit (582).

Muscular conductance and resistance arteries are richer in SMCs that are highly interconnected by cell-cell junctions in a looser collagen network (resistance artery). Distal arterial and arteriolar tapering is the anatomic and functional site of high mechanical energy dissipation due to peripheral frictional forces, a drag that protects the downstream capillary compartment from high blood velocities and pressure, favoring tissue transport of energetic substrates (diffusion from nonpressurized capillaries to metabolically active tissues). It is also the distal site of energy transfer in which viscous frictional forces of flow cause it to backscatter upstream as a distal reflective pressure wave. Conductance arteries are the main sites of other noncontractile components of circulatory impedance, i.e., SMC tensegrity, compliance and rigidity, branching, pressure wave reflections, and flow oscillations.

A. Vasomotricity Determines Frictional Forces and Arterial Pressure (FIGURE 5, Poiseuille Law)

Since the circulation in mammals is a closed mechanical system, and temperature constant, the first law of thermodynamics (mechanical energy conservation) could be approximatively applicable, involving both kinetic (Ek) and potential (Ep) energy in mammals. Therefore different energetics, involving heat transformation of Ek, storage of Ep, transfer from Ep to Ek, but also inversely from Ek to Ep and dissipation of both are present in the circulation of mammals.

The peripheral resistances to flow comprises the frictional forces that viscous blood exerts on the vessel wall depending on its geometry. As evolution progresses, the arterial frictional forces are not only determined by anatomy as in fish but are mainly due to SMC arterial function, related to the contractile tone of the wall in muscular and resistance arteries. In contrast, the venous system and the pulmonary circulation remain essentially areas of flow without important resistance. An additional role of bifurcations in this definition of arterial pressure cannot be excluded (see below). Frictional forces also contribute to energy dissipation, participating in a small way in the generation of heat and endothermy and, importantly, contributing to upstream pressure. Viscous frictional forces do not only impact the wall but also the blood rheology, the interactions between the particulate components of the blood (circulating cells), but also some plasma components such as vWF for instance (see sect. VIC and Ref. 233 for more details).

The usual view of the Poiseuille law considers the pressure gradient (dp) as the driving force for volume laminar flow rate (q_v) (Ep to Ek transfer) through a regular tube length (l) with a constant radius (r) and with constant frictional forces linked to the dynamic viscosity of the blood (η) **(FIGURE 5)**. In the evolutionary view, we must consider the frictional forces proportional to flow (q_v), viscosity (η) and length (l) and inversely proportional to the radius power four (dr^4) as the determinant of both upstream blood pressure (https://www.syvum.com/cgi/online/serve.cgi/eng/fluid/fluid203.html for a more mathematical demonstration) and downstream dissipation of mechanical energy protecting the capillary exchange compartment. Therefore, a small progressive functional decrease in internal radius along the arterial tree increases the frictional forces and determines a high arterial blood pressure. This is mainly due to the small muscular arteries and arterioles (contractile tone) under control of the sympathetic tone. The high arterial pressure

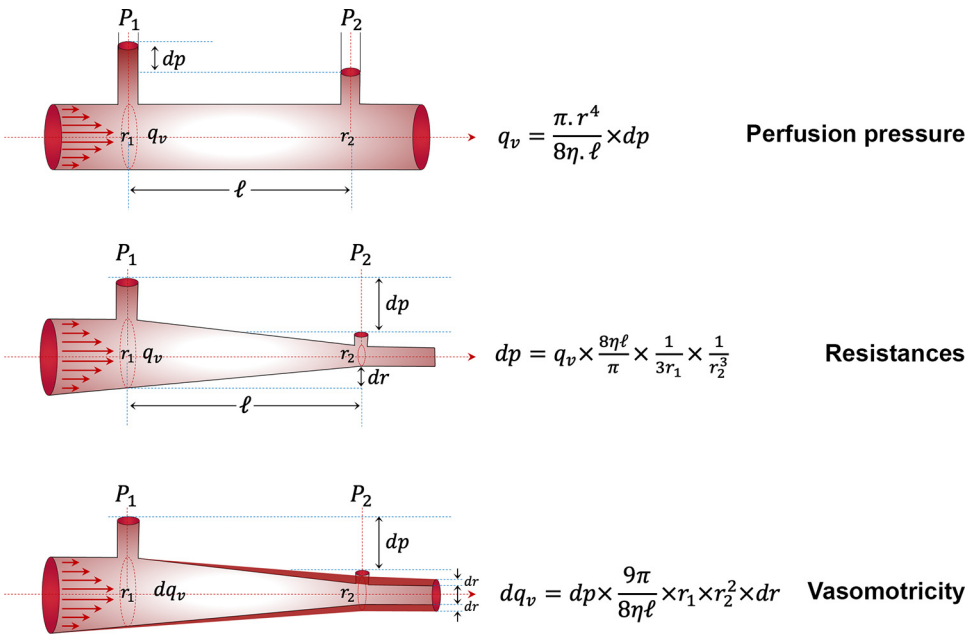

FIGURE 5. Three representations of the Poiseuille law in relation to 3 different functions of the flow-dependent viscous frictional forces. *Top*: the canonical representation of the Poiseuille law in which the pressure gradient determines the flow dragged by the viscous frictional force. *Middle*: the tapering of the radius determines the resistance to flow, and therefore the upstream pressure. *Bottom*: how a small variation in radius defines vasomotricity and therefore the local variation in flow.

(120–80 mmHg) is the main evolutionary acquisition of the circulation in mammals. In this paradigm, systemic arterial blood pressure (energy transfer) upstream and local energy dissipation downstream are due to the progressive functional tapering of arterial lumen and topological changes in wall geometry.

To assume this high pressurization in the arterial part of the circulation, the structure and contractile functions of the muscular arteries and arterioles differ from that of elastic arteries by wall tissue morphology, SMC density, contractility, connectivity, and molecular patterns of regulation [see outward conductance of soluble mediators, sect. VI*B* (386) for more complete description]. Whereas the wall of conductance elastic arteries is organized as lamellar units associating one layer of SMCs with one elastic lamina and intermediate collagens and glycoproteins, resistance arteries are organized as an interconnected assembly of adjacent SMCs, limited inside by the internal elastic lamina and limited or not outside by an external elastic lamina. In this structural context, the function of resistance to flow is predominantly assumed through connective gap junction channels between adjacent SMCs, allowing the spreading of the contractile signal throughout the SMCs. These intercellular channels are composed of connexins (Cx), a family of 21 members in humans in which Cx43, Cx45, and sometimes Cx37 are present in vascular SMCs (433). These channels allow the passage of small molecules, such as Ca^{2+} and other ions, signaling molecules, inositol-phosphate (IP), NAD^{+}, ATP, cyclic nucleotides, miRNA, etc. Variable intracellular COOH-terminal domains of connexins interact with numerous other regulating cytoplasmic molecules (reviewed in Refs. 368, 433). Electrical signals (depolarization waves) also diffuse through gap junctions participating in the spreading of the contractile tone generated at the "functional syncytium" of the external interface of the media receiving sympathetic innervation (101). Gap junctions and connexins also connect endothelial cells with SMCs via holes in the internal elastic lamina in resistance arteries and arterioles (21, 471). Therefore, SMC-dependent arterial vasomotor tone is tightly controlled by gap junction permeability involving phosphorylation of the intracellular domains of connexin but also mechanotransduction via connexin/fibrillar cytoskeletal interactions (249, 315). This effect plays an important role in myogenic tone (see sect. III, *G* and *H*).

In summary, frictional forces play important, and sometimes opposite, roles in arterial circulation, as follows:

- By regulating endothelium-dependent vasomotricity in conductance arteries (see sect. III*E*, **FIGURE 4*C***)
- By producing arteriolar drag to limit blood velocity and pressure in capillaries (see below myogenic response and energy dissipation)
- As the main determinant of systemic arterial pressure
- By regulating vascular coupling to organ function by their localized decrease (see sect. III*D*)
- As the main determinant of angiogenesis and arteriogenesis during fetal life.

SMC contractile tones in the arterial and/or arteriolar walls are the main monitors of frictional forces.

B. Branching, Reflection Waves, and Impedance

The existence of arborescence in the arterial circulation also raises the question of the relationship of dimension and angle of the bifurcations between the mother and the branching arteries (384). This question is subject to the rule of minimal work. In this context, the aorta appears disproportionally large, but it acts as a secondary elastic reservoir that accumulates potential energy in systole that it restitutes as flow during diastole, buffering the phasic potential energy generated by the left ventricular ejection, therefore participating in achieving "minimal work" (385). Thus aortic compliance and elasticity is an example of mechanical energy transfer from pressure to flow, but also potential energy stress and dissipation within the aortic wall at the peak of pressure (see below convection), repeated 3 billion times during a life of 80 yr. The tradeoff is that the pulsatile tensile stress is particularly high in the aorta in relation to its large radius (Laplace law), and the aortic SMCs are highly stretched and strained at each systole.

One of the questions raised by proximal hemodynamics is the differential between the pressure wave form and flow wave form in the aorta (563). To put it simply, the outflow wave is limited to ejection time (systole), whereas the pressure wave form is also maximal in systole but slowly (exponentially) decreases during diastole. Today, biomechanical models of the pressure waveform consider that there is a basic (reservoir) blood pressure and resistance, mainly related to blood volume inertia during diastole, in which the systolic ejected outflow abruptly generates a compressive force wave that propagates along the arterial tree (for review, see Ref. 542). The velocity of this propagated pressure wave (pulse wave velocity, PWV) through conductance arteries is a marker of wall rigidity: the more compliant (elastic) the wall, the more the pulse wave is dampened and propagated slowly, and conversely, the more rigid the arterial wall, the higher the PWV. This hemodynamic marker is largely used in clinical medicine, for instance, to evaluate the rigidity of the arterial wall in hypertension and aging (292) (see sect. VI*F*).

All partial obstructions to flow, whether anatomical (bifurcations, narrowing) or functional (vasoconstriction, tapering, wall rigidity, viscous drag), increase general and/or local frictional forces and dissipation, generating "reflection" pressure waves. The role of bifurcations in these reflection

waves has been remarkably exemplified by Alberto Avolio and colleagues in comparative studies of the central pressure curve in the snake (python), which has a streamlined aorta with orthogonally branched small arterial collaterals, and the kangaroo, in which the lower part of the body is highly muscular with a large number of arterial bifurcations and muscular arterial terminations. In the python, the diastolic pressure curve decreases regularly without rebound (25), whereas the central pressure curve of the kangaroo presents a protodiastolic rebound, with a peak intensity superior to the systolic rebound (24) **(FIGURE 6)**, corresponding to the python's systolic pressure curve with the addition of the delayed reflective wave in diastole. At any arterial bifurcation, the flow impingement and energy dissipation within the arterial wall are dependent on the flow velocity and the relationship between the respective calibers and angles of the upstream artery and the branches. In this context, pressure reflection waves could be considered as an energetic transfer from Ek to Ep. More proximal reflection waves, due to aortic rigidity, enhance the systolic peak pressure, increasing the differential systolo-diastolic pressure, a phenomenon usually observed with aging. Such general or local dissipative impingements and reflection waves play important roles in aging and in site-specific pathologies (atheroma, aneurysms, see below), respectively.

The relationship between phasic flow and phasic pressure in conductance arteries can be represented by harmonic analysis (Fourier transformations) and the relation of sinusoid decomposition of pressure to sinusoid decomposition of flow. Impedance in the blood circulation is a measure of how the arterial system resists the motion imposed by phasic flow and the associated phasic forces related to viscosity, inertia of blood capacitance and wall elasticity, also dependent on heart rate. Impedance in the arterial system can be general, usually measured in the aorta, or localized at specific points. For example, bifurcations or stenoses and poststenotic dilations may be considered as localized hot spots in which dissipative forces [dispersion of velocity vectors, loss of laminar flow, transverse wall shear stress (367)] increase the dissipation of mechanical (Ek and Ep) energies within the wall. Finally, the combination of hemodynamic elements defining local and general impedance (frictional forces, inertia of the blood mass, rigidity or elasticity of the

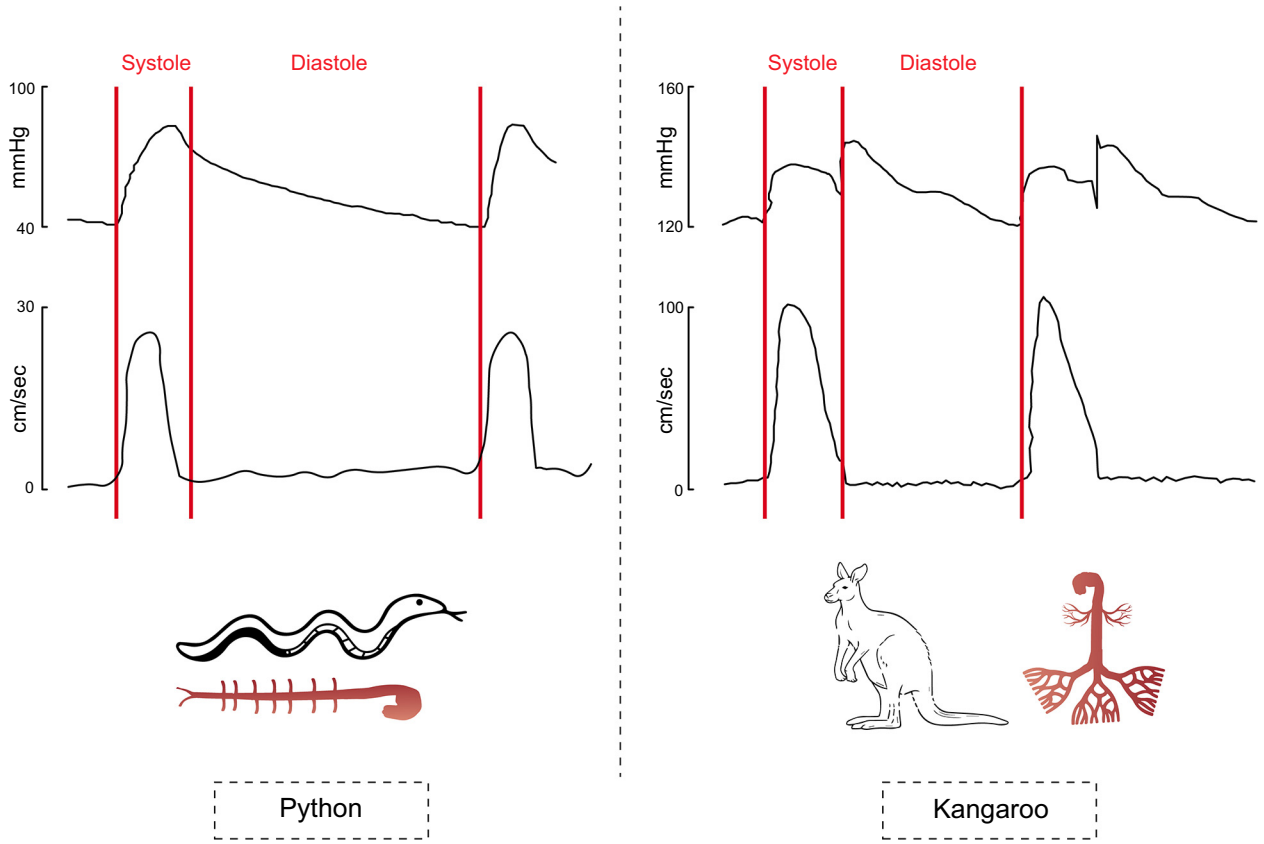

FIGURE 6. The role of bifurcations in pressure reflection waves. In the python, blood flow is essentially laminar and does not generate important reflection waves. Therefore, diastolic pressure declines regularly. In the kangaroo, due to the considerable development of striated muscle of hindlegs and tail, the circulation of the lower limbs is highly developed and arborescent (multiple bifurcations, loss of flow laminarity), whereas the anterior limbs and the upper circulation have regressed. This special architecture induces a high level of flow-generated pressure reflection waves (kinetic energy dissipation and transfer), which promote a delayed (with respect of left ventricular ejection) protodiastolic peak of pressure, higher than the systolic one. [Redrawn from Avolio et al. (25), Avolio et al. (26), and Nichols et al. (394).]

arterial wall, reflection waves, etc.) is the main determinant of the energy transfer, from Ek to Ep, the most important hemodynamic acquisition in the evolution of species from teleosts to mature mammals.

C. Sympathetic Influx Determines Contractile Tone of the Arterial Media (FIGURE 4*C*)

In mammals, arteries are innervated by postganglionic sympathetic fibers, which develop in the adventitia, the outer layer of the arterial wall, and interact with the SMCs through the external elastic lamina. The innervation density increases as the arterial diameter decreases. Sympathetic innervation is the main determinant of the arterial contractile tone via release of catecholamines in the synapses between neurons and SMCs. These neurotransmitters act through the α1 adrenergic receptors, inducing phospholipase C activation, the intracellular release of inositol phosphates, calcium entry, the formation of calcium-calmodulin complexes, the translocation of protein kinase C (PKC) to membranous diacylglycerol, the phosphorylation of numerous contractile proteins (myosin light chain, calponin, caldesmon), and inactivation of phosphatases (rho kinase) (311). All these mechanisms are dependent on phosphoryl transfers to contractile proteins, using ATP or GTP as energetic substrates, which are both produced by mitochondria (O_2 consumption) through electron transport. Therefore, mitochondria are permanently stimulated in arterial SMCs to produce ATP and GTP for maintaining the arterial tone (sliding of actomyosin), but also spontaneously release free electrons (e^-) and reactive oxygen species (ROS) and produce heat proportional to their activity. Free e^- and O_2^- are permanently chelated by superoxide dismutase (SOD2, $OH^- + O_2$) (612). In contrast to myocardial phasic contraction, in which calcium entry could directly bind to troponin C and activate the contractile apparatus (excitation-contraction coupling), there is no direct action of Ca^{2+} on SMC tonic contraction. All the molecular mechanisms are indirect, mediated by Ca-calmodulin complex and kinases, phosphorylating and dephosphorylating target proteins associated with actomyosin (myosin light-chain kinase and phosphatase, caldesmon, calponin, etc.). Of note, a similar signaling pathway (Ca-calmodulin complex and kinases) controls the endothelial cell activity by stimulating nitric oxide (NO) synthase, inducing subjacent SMC relaxation and vasodilation (349).

In the arterial media, the inward sympathetic tone spreads from outside to inside by diffusion of second messengers (Ca^{2+}, inositol phosphates) via connexins through the SMC network of muscular and resistance arteries, maintaining contractile tone. Contractile tone is more important in small than in large arteries because of the denser innervation and the easier inward and longitudinal diffusion of the contractile second messengers via the denser SMC connections, which increase with the reduction in arterial diameter and the decreased amount of ECM interposed between cells.

The interactions of sympathetic innervation with the arterial wall are not limited to SMC contractile tone. Arterial SMCs also participate in the development of the sympathetic axons through the outward release of neurotrophic factors (135), signaling for guidance and function of the axons along the arterial tree. Conversely, sympathetic tone contributes to the differentiation of contractile SMCs, arterial maturation, and wall structure (505).

Arterial blood pressure remains relatively constant in humans, despite the changes from supine to upright postures and back. This is largely due to the baroreflex, which senses blood pressure changes in the carotid sinus, protecting the brain from perfusion pressure variability by compensating for increased gravitational forces (160). The upright posture was acquired fairly late in the great apes, in parallel with the considerable development and diversification of cerebral activities, including the adaptation of the anatomy (456) and physiology of the cerebral circulation. Arterial adaptation to cognitive functions in humans (410) was and remains one (perhaps THE one) of, if not THE major challenges for understanding the dynamics of evolution of the brain (a full comprehensive synthesis of this question remains out of the scope of the present review). Numerous physiological reviews have dealt with the question of cerebral blood flow and its regulation, the blood-brain barrier, orthostatism, etc. (see Refs. 230 and 516 for recent reviews). For understanding cerebral blood flow regulation as an adaptation of the perfusion pressure to gravitational forces of the perfusion pressure, the baroreflex, the heart and the venous system in giraffes are of particular interest (363). Because their intracranial circulation is continuously exposed to variations in gravitational forces and cerebral blood flow, giraffes have a highly functional baroreceptor system (273). They generate sufficient arterial perfusion pressure at the top of the neck to permanently ensure sufficient cerebral blood flow against gravitational forces. This energetic and territorial transfer is ensured by the redistribution of peripheral resistances, involving an important muscularization of the leg arteries (362). These observations suggest that the central nervous system controls perfusion pressure and blood flow in the brain. Furthermore, these observations support the Harvey Cushing theory (110) that brain perfusion regulates systemic arterial pressure. This concept is of importance in humans (421), since the evolutionary development of brain cognitive functions will require more and more specifically localized blood flow.

Accordingly, this predominant role of the baroreflex, transmitted by the carotid sinus nerve (436), has led to the proposal of baroreceptor-activating therapy, in which chronic stimulation of the nerve by electrodes decreases resistant hypertension

(116, 598). Nevertheless, the cost-effectiveness ratio of this new technology remains controversial (431).

Another important phenomenon associated with the pressure-dependent stretching of the muscular arteries and arterioles is the myogenic tone: in response to pressure-dependent acute change in tensile stress, more Ca^{2+} enters the SMCs and leads to actomyosin activation and SMC contraction (277). This phenomenon is well-described ex vivo in small resistance arteries, in which it dampens the pressure wave and drags the flow wave, protecting the capillaries from any acute increase in mechanical strength. Recently the determinants of the myogenic tone have been extended to pulsatile pressure which induce cyclic stretching ex vivo in the mouse posterior cerebral artery (441). The data show a positive interaction between pulse pressure, myogenic contraction, and flow-mediated vasodilation. This interaction involved endothelial NO modulation.

The SMC contractile response to acute change in pressure in elastic arteries is less documented. Nevertheless, it has been shown that active contractile tone in response to increased passive stretching prevents delamination of the aorta in mice sensitized to acute dissection (152). Both calcium channels and G protein receptors are involved in this response to stretch (266). The integrality of the cytoskeleton, including actomyosin sliding, and its link to the cell membrane and the calcium channels are necessary for this phenomenon (452). Strengthening of the myogenic tone in response to acute increase in blood pressure potentially existing in conductance arteries is a necessity for preventing delamination. This has been observed in vitro in cultured SMCs (53) and the rat aorta in vivo, particularly in the context of hypertension (443), but has not yet been clearly demonstrated in humans.

D. Coupling Between Metabolic Activities and Local Vasodilatation Within Tissues

The means of coupling the functional activities of regional territories with their metabolic support (oxygen, glucose, others) conveyed by the arterial circulation towards the tissue capillaries are diverse. Servo-controlled signals are generated by functional activities and diffused to local vessels, including arterioles and capillaries. In this way, vasodilator signaling reaches the vessel wall via its external or internal layers, which may involve pericytes and capillary endothelium as well as the SMCs themselves. In this architecture, the potential signaling of endothelial activity spreads upstream via gap junctions between endothelial cells, transmitting Ca^{2+} signaling via Ca^{2+}-dependent potassium channels, endothelium-dependent hyperpolarization, and release of NO, C-type natriuretic peptide (499), and prostacyclin (571). Since functional activities are diverse, the signals are also numerous and dependent on the specificities of organ function. For instance, the tissue signal may be directly linked to metabolic activity.

This is the case for striated muscle contraction, a process that induces the highest changes in the circulation in the body (exercise). Muscle contraction is highly ATP-consumptive, generating adenosine, which can diffuse out of the muscle cells into the tissue interstitium (375). Adenosine signals to the arteriolar SMCs via the adenosine receptor, coupled to the intracellular adenylate pathway that generates cAMP, a powerful inhibitor of calcium mobilization within SMCs (372). In this context, blocking adenosine catabolism by an adenosine deaminase antagonist (carbo/chlorichromene) potentiates adenosine action and promotes arteriolar relaxation. Carbochromene was used experimentally for many years to measure the coronary flow reserve (difference in coronary flow before and after carbochromene injection) (32).

Conversely, neurovascular coupling in the brain is probably not directly dependent on neuronal energetic metabolism. Numerous mediators have been suggested: NO produced by calcium-dependent neuronal NO synthase activity, prostaglandin E_2 produced by phospholipase activities, etc. It was recently proposed that the coupling between neuronal electrical activity and vasodilation is distally generated, mainly involving pericyte relaxation (205) at the capillary level and astrocyte activation (361). For instance, pericyte degeneration leads to neurovascular uncoupling (274).

This distal neurovascular coupling allows the use of blood-oxygen-level-dependent (BOLD) signaling in MRI to precisely localize neuronal activity (310). In this context, capillaries dilate before arterioles, in which the secondary dilation is potentially linked to NO release by the endothelium. In fact, vasodilating signals spread retrogradely upstream from the active distal tissues to the more proximal arteries via interendothelial gap junctions and upstream propagation of depolarizing electrical charges, and possibly also through endothelial-SMC gap junctions and connexins (571) **(FIGURE 4*C*)**. This phenomenon of retroconduction in resistance arterioles and arteries was described 100 years ago (285). The retroconducted (from downstream to upstream) vasodilator response to increased organ functions in resistance arteries was demonstrated to be inherent to the arterial wall, independent of both sympathetic and parasympathetic innervation and of hemodynamics (pressure and flow) (476) but dependent on endothelial cell interconnectivity (gap junction) (477).

E. Flow-Dependent Outward Vasodilator Function in Conductance and Muscular Arteries

As in fishes, the phasic flow in conductance and muscular arteries induces frictional forces on the most luminal layer

of the wall. This phasic shear (τ = fct $\eta V/r$) maintains the basic production of NO by the endothelium, which outwardly signals relaxation to subjacent SMCs by partly inhibiting the calcium mobilization produced by the inward sympathetic tone **(FIGURE 4*C*)**. The intensity of relaxation is proportional to the biomechanical shear stress on the endothelium. The mechanotransduction of shear on the endothelial surface is ensured by mechanosensitive molecules [reviewed in Ref. 33, including estrogen receptors in the female (526, 527)]. In this molecular endothelial context, loss of caveolin-NO synthase inhibitor interactions due to mobilization of calcium-calmodulin (150) leads to more NO release and endothelium-dependent local vasodilation by the activation of soluble guanylate cyclase in subjacent SMCs (20). If the high flow stimulus is sustained, the arterial wall structurally outwardly remodel, increasing radius (109). Similarly, the increasing flow in collateral vessels related to ischemic territory induces collateral vessel growth and outward remodeling (257, 294).

Conversely, the global pharmacological inhibition of endothelial NO synthase by an arginine antagonist (N^G-nitro-L-arginine methyl ester, L-NAME) induces hypertension (20) by reinforcing the vasoconstrictor tone in resistance arteries (126, 222). In this context, the limit between flow-dependent and depolarization-dependent vasodilations, which are both endothelium dependent, is difficult to define precisely. For example, animals chronically intoxicated by L-NAME develop monoplegic neurological deficits and die from occlusive arteriolopathies in the CNS, rather than from proximal artery diseases (52). This observation fits well with a distal role of endothelium-dependent, NO-mediated vasodilation in distal arteries. This arteriolopathy is diffuse and not limited to the brain but also affects the kidney (587) and other organs.

F. Wall Tensile Biomechanical Stress (FIGURE 7)

Although generated by frictional forces, the acquired arterial pressure is a source of new tensile stress in addition to frictional forces (shear stress). This stress corresponds to the force exerted by pressure (Ep) within the arterial dimensions. According to the law of Laplace, this radial tensile force is tangential to the wall, proportional to the pressure and the radius, and quantitatively distributed throughout the wall thickness, including the SMCs, and qualitatively supported mainly by the fibrillar ECM, which itself is synthesized and matured by the SMCs. The tensile stress appears after birth (see above) and is also exerted longitudinally. Moreover, the wall tensile stress is sinusoidal with a systolic peak and an incomplete diastolic recoil. This phasic sinusoidal form defines pressure pulsatility. In this context, the biomechanical "fatigue" of the wall is proportional to the stress peak intensity multiplied by the frequency of the peak and the length of time. The peak of tensile stress and its diastolic recoil mechanically and cyclically stretch the arterial wall 3×10^9 times during a human lifetime of 80 yr.

The ECM constituents are biopolymers, which define the major structural and functional characteristics of the arterial wall, including the large-conductance arteries and the muscular and resistance arteries. ECM is composed of a network of different macrofibrillar proteins involving mainly elastin and collagens, internally reinforced by lysine-oxidase (LOX-1) covalent bridges (desmosine isodes-

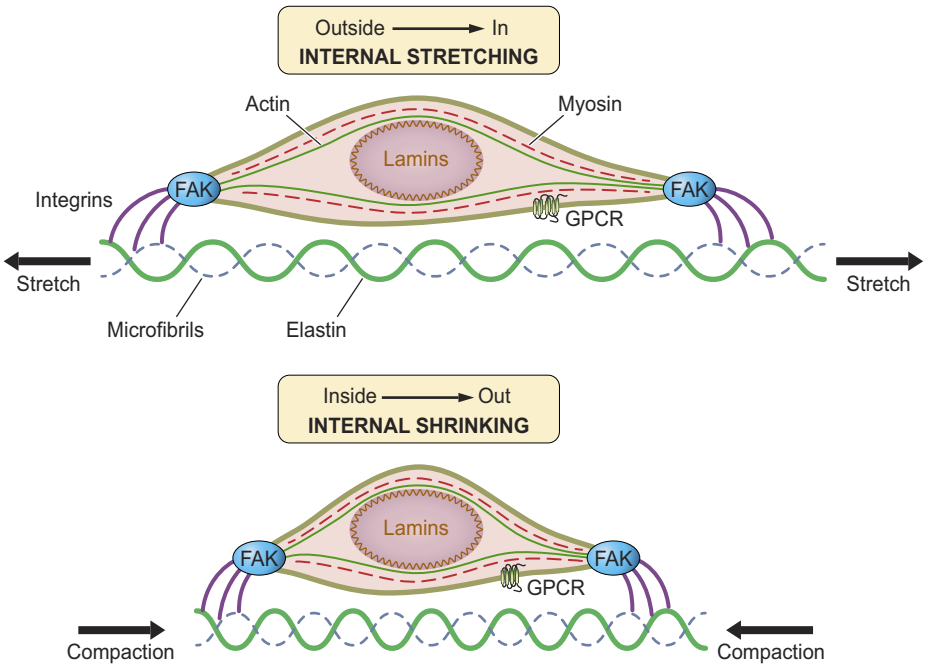

FIGURE 7. Mechanotransductions. The mechanotransduction in smooth muscle cells (SMCs) can be deciphered with respect to dual extrinsic (hemodynamic dependent) and intrinsic (actomyosin activation) mechanisms. The former, from outside to inside SMCs, deals with the initial stretch of the extracellular matrix, particularly elastic laminae in the large arteries, which is transmitted via integrins, focal adhesion kinase (FAK) and G protein-coupled receptor (GPCR), to the cytoskeleton and nuclear envelope, able to (re)model the chromatin architecture, changing the constitutive pattern of gene expression. The latter, from inside to outside, is initiated by the sliding of myosin on actin leading to shortening of the cytoskeleton, the shrinking of SMCs, and finally to the compaction of the wall tissue. The effects of this duality on cell and tissue physiology are quite different: stretch versus shortening and distension versus compaction.

mosine) (131), rendering them insoluble. Elastin is composed of a succession of hydrophobic domains, in which entropic forces generate the recoil phenomenon, and cross-linking domains, which confer solidity to the biopolymer. Intermediate glycoproteins, such as fibronectin, fibrillin, fibulin, microfibril associated glycoproteins (MAGPs), and elastin microfibril interface located protein (EMILIN), and proteoglycans are also members of the ECM (560). The elastin fiber recoil plays the major role in distensibility, compliance, and pulsatility of conductance arteries. Elastic laminas are circumferentially layered between sheets of SMCs. Proximal conductance arteries, particularly the aorta and its main branches, are enriched in elastin, providing the wall with considerable compliance and elasticity to allow functional dilation in systole and energy restitution in diastole (Windkessel effect). This process has been analogically modelized as a circuit involving the potential difference of in-parallel resistances and capacitances (573). In conductance arteries, elastin is qualitatively involved mainly in wall resistance to pressure-dependent dilation, whereas collagen is implicated in resistance to rupture (123).

Moreover, the ECM is able to retain different growth factors, such as transforming growth factor (TGF)-β, associated with latent binding protein (LTBP), which is anchored to fibrillin and fibronectin. In this physiological context, canonical TGF-β signaling in SMCs is adapted: in response to functional ECM distension and/or to structural ECM injury (proteolysis), TGF-β is released from its ECM storage sites. TGF-β interacts with its receptors expressed on SMC, inducing nuclear translocation of phosphorylated Smad2 and Smad3, as Smad3 is mainly involved in ECM production. Interesting enough, more than 10 years ago, Bressan et al. (66) at the university of Padua demonstrated that Emilin-1, an intermediary glycoprotein directly associated with elastin in the ECM, is able to limit TGF-β activities (impairment of pro-TGF-β maturation by furin convertase) (599). Moreover, intriguingly, Emilin-1 suppression in mice generated a higher blood pressure, which was rescued by blocking TGF-β (599). This functional effect appears to be related to enhancement of the myogenic tone, through transactivation of epidermal growth factor signaling (86). These biological data were confirmed at a phenotype level (514) and genetic risk (487) in human. Of note, the family of bone morphogenic protein (a member of TGF-β family) is directly involved in pulmonary hypertension (187).

TGF-β also increases the expression of reparative genes as LOX-1, and antiproteases (186). Other growth factors are retained by glycosaminoglycans (heparinoids) (91). SMCs synthesize ECM proteins but are also able to synthesize some serine proteases [tissue-type plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), and their inhibitors (tissue-serpins, Ref. 61)] and, constitutively, some matrix metalloproteinases (MMPs) such as pro-MMP2 (42) and their tissue inhibitors (TIMPs) (164).

Intermediate glycoproteins, such as fibronectin, fibrillin, and proteoglycans, etc., are also members of the ECM. Numerous proteins of the ECM scaffolding, particularly fibronectin, vitronectin, and fibrin for healing, present arginine-glycine-aspartate (R-G-D) motifs in their protein sequence, which are binding sites for integrins (34). In contrast to elastin fibrils which cannot be directly used as an adhesive substrate for SMC, due to their high degree of hydrophobicity, collagen can act as an adhesive substrate for numerous types of cells (epithelial cells, endothelial cells, etc. (see Ref. 442 for extended review). The adhesive sequence on collagen is a glycine-phenylalanine-hydroxyproline-glycine-glutamate-arginine (CFOGER) motif (276). Integrins are heterodimeric, full transmembrane proteins containing noncovalently associated α and β chains (241). Integrins are heterodimeric, full transmembrane proteins containing noncovalently associated α and β chains (241). The α-subunit is directly involved in ligand specificity, whereas the β-subunit supports the connection with the cytoskeleton and is involved in mechanotransduction signals. Proteolytic impairment of these adhesive interactions between ECM and integrins causes cell detachment and apoptosis (338), a biological process named anoikis (345), which may be involved in the disappearance of SMCs.

In addition to tensile stress generated by ECM stretching and recoil, internal tensegrity and actomyosin sliding also generate an internal mechanical stress, not only shortening the SMC itself, but also the ECM, leading to compaction of the full arterial wall **(FIGURE 7)**. Conversely, relaxation of the SMC creates decompaction of the arterial tissue. Compaction decreases the water content and the wall permeability, whereas decompaction has the opposite effect, potentially promoting delamination in the media of conductance arteries (see sect. V*B*).

G. SMC Mechanotransduction

Throughout life, SMCs support a basic tonic stretching (mean arterial tension) that sinusoidally fluctuates (pulsatility) proportionally to the variation in pressure and dimension (Laplace law). As described above, peptidic sequences in the ECM fibrillar components and integrins are the main actors of cell adhesion and therefore of mechanotransduction from the ECM to SMCs. Focal adhesions, corresponding to the clustering of integrins in some specific areas of the SMC membranes, are mainly responsible for the out-in transduction of biomechanical signals (76). Focal adhesions provide the link between integrins and the intracellular cytoskeleton, composed mainly of actin and actomyosin complexes. Focal adhesions are enriched in actinin, which serves to anchor actin to the integrin intracellular domain; vinculin, which coaligns with fibronectin fibrils on the cell surface

(77); talin, which is involved in integrin activation, promoting their interactions with the ECM (34); focal adhesion kinase (FAK; targeting Jnk, Erk, and phosphatidylinositol 3-kinase pathways) and some other proteins (76). Integrin clustering and ECM engagement triggers tyrosine phosphorylation in multiple intracellular targets involving this adhesion pathway in numerous cell processes, including adherent cell survival, growth and proliferation, differentiation and phenotypic switch, etc. In parallel, RhoA, a small GTPase associated with focal adhesions, regulates cytoskeletal structure and activity, actomyosin stress fiber formation (internal tensile stress), and actomyosin sliding in SMC contraction (321). It is noteworthy the myogenic response of SMCs to a biomechanical stimulus is 100 times faster (300 ms) than a similar response to a biochemical ligand/receptor interaction (>30 s) (388, 434).

In addition to the integrin pathway, G protein-coupled receptors (GPCRs) are also mechanosensitive pathways independent of the canonical ligand-receptor pathways. In this context the angiotensin II type 1 (AT1R) has been the most studied (472). This effect appears to be mediated by β-arrestin engagement in AT1R via the inhibitory G protein ($G\alpha_i$) (562). These data can be compared with some mutations within the seven transmembrane domains, leading to constitutive activation of the AT1R (429). When the receptor is molecularly constrained, it is inactive. The pharmacological agonist, gain-of-function mutations, and potentially the membrane stretching, all lead to AT1R activation by relaxing conformation in the transmembrane domains and internalization by binding to β-arrestin (429).

Inside the cells, the cytoskeleton is the main cytosolic component generating the internal tensile stress that supports stretching (stress fiber) (78). The cytoskeleton is an assembly of biopolymers: actin and myosin forming actomyosin filaments and stress fibers, microtubules and intermediate filaments [vimentin, desmin (523), filamin (445), and inducible nestin (81)] forming the scaffolding of adherent cells. Nuclear lamins are also intermediate filaments, subjacent to the inner nuclear membrane, forming with it the nuclear envelope and the scaffolding for nuclear shape and structure and participating in nuclear function (517).

1. Actin

Polymerization of globular monomeric (G-) to fibrillar polymeric (F-) actin and subsequent depolymerization plays a major role in numerous processes involved in morphological and functional SMC plasticity (cytokinesis, SMC migration, endocytosis and phagocytosis, adhesion and contraction, etc.) (461). Actin is an ancient, highly evolutionarily conserved protein polymer that is present in prokaryotes, a fact that explains its presence not only in the cytoplasm but also in the nucleus (30). In the nucleus, G-actin is associated with RNA polymerase and is involved in transcription initiation, elongation, and inhibition of serum responsive factor (SRF) activation (30). Nuclear β-actin also interacts with HAT (400) and histone deacetylase (HDAC) (481) and globally plays a major role in chromatin organization and gene expression (585). F-actin is also present in the nucleus as highly flexible short filaments (30). In humans, there are six actin isoforms including α- (Acta2, SMC), α-skeletal (Acta1), and α-cardiac (Actc1) striated muscle actins (548). Acta2 is predominant in SMCs, but β-actin is also present, participating in the cytoskeletal architecture, mechanotransduction, vasomotricity (actomyosin sliding), and SMC plasticity. Importantly, SMCs must form podosomes, predominantly involving actin, in response to numerous physiological or pathological cues [spreading, increased pressure, stretching, response to growth factors (200)], finally promoting localized pericellular proteolysis and motility (73) leading to inward migration of medial SMCs and intimal proliferation (271). Other components of the cytoskeleton are involved in podosome formation, including caldesmon (140, 199) and microtubules (614). Of note, podosome formation is associated with actin isoform reorganization, partial loss of F-actin, and podosome relocalization of Acta2 and β-actin in response to phorbol dibutyrate, whereas stimulus cessation reverses the phenomenon, reestablishing actomyosin stress fibers (69). These molecular switches in actin balance correspond to associated phenotypic switching between contractile and migratory functions, proliferative and synthetic phenotypes of SMCs, defining at least in part their plasticity. In parallel, SMCs have also acquired a SM-specific myosin isoform (MYH11) (180). Among up to 35 classes of myosins, the smooth muscle myosin isoform is mechanically characterized by a tonic action rather than a fast one as for cardiac and striated muscle. The biochemical interactions are also quite different (caldesmon, calponin, transgellin...) from those of sarcomeric myosin. Lastly, the regulation of contraction is different: in cardiac muscle, Ca^{2+} directly bind troponin in the actomyosin apparatus, whereas the Ca^{2+}- calmodulin complex activates kinase and targets phosphorylation of regulating proteins. Therefore, the contraction/relaxation consumption of ATP is high in SMC (51, 515).

2. Biomechanical modeling

Different models have been proposed for integrating biomechanics in cell biology. The first was the tensegrity model proposed by Ingber (244) as an intracellular lattice architecture of compressive (struts) and tensile elements (cables). In this model, tensile cables are mainly represented by actomyosin, whereas compressive struts are represented by microtubules (246). Intermediate filaments are more elastic, undergoing entropic conformational changes depending on the tensile stress level. This elasticity is mainly recruited when the cell is highly stretched, and the intermediate filaments are extended. The intermediate filaments directly support the structure and function of the cell membranes. The main thermodynamic point is that these intracellular

elements are basically prestressed, consuming ATP and GTP as their energy source (oxidative metabolism). In this context, ECM rigidity increases internal tensegrity by resisting the cell's internal tensile force.

The second model is the soft glass rheology model (463), which is now recognized as a relevant dynamic model for mechanotransduction within the target cells. Depending on energy cost, the metastable intracellular cytoskeleton can oscillate between a solid, static network and a more fluid rheological behavior (141, 541). This paradigm is relevant for arterial SMCs, which are permanently exposed to cyclic stretching and release, and important phenotypic changes.

3. Myogenic response

The energy-consumptive maintenance of tensile force of the internal cytoskeleton and its dynamics are constitutively involved in all SMC functions: adhesion to ECM, tonic contraction, cell shape and deformation, migration and proliferation, differentiation, endo/phagocytosis, and phenotypic shifts (291). In the hemodynamic context, one of the main effects of cytoskeletal tensile stress on SMC physiology is the opening of membrane ion channels, inducing Ca^{2+} flux entry and myogenic tone in small arteries. For instance, it was recently shown that filamin A (445), an intermediate filament bound to actin, is a necessary molecular intermediary between change in pressure, stress-dependent Piezo1 calcium channel, and the myogenic response (452).

As for cell-to-cell vasomotor signal spreading via gap junctions in resistance arteries, mechanotransduction also involves cell-to-cell communication in the walls of resistance arteries. Intercellular adherens and tight junctions are mainly assured by N-cadherin (512). Cadherins possess a large extracellular part with five repeated (EC1 to 5) domains. EC1 and 2 *trans*-bind N-cadherin EC1 of the adjacent cell and *cis*-interact with nearby cadherins. The intracellular domain binds catenins and, indirectly, vinculin and cytoskeletal F-actin. N-cadherin is directly involved in the myogenic response to mechanical stimuli and in the vasomotor tone in response to pharmacological agonists (511) in resistance arteries and arterioles.

Therefore, we can conclude that adhesion of SMCs to ECM, integrin clustering, and the cytoskeleton all play predominant roles in mechanotransduction in ECM-rich conductance arteries, whereas collective SMCs, tight junctions, cadherin, and GPCR play a predominant role in resistance arteries and myogenic tone. Moreover, the two adhesion signaling pathways, ECM and intercellular adhesions, exert negative feedback on each other (79). This crosstalk between the two adhesion systems is also potentially important for understanding mechanotransduction in walls of different arterial compartments (conductance vs. resistance) (328, 340). In contrast, the myogenic responses in large elastic arteries are less documented but are potential determinants of aneurysmal risk and delamination leading to dissections (240).

In this cellular and molecular context, the involvement of mitochondrial bioenergetic and cytosolic NADPH oxidase (NOX) activities regulating the basal redox state of the cell, or leading to oxidative stress, are long-term determinants of SMC functions, survival, and pathology. Mitochondrial dynamics involving mitochondrial fusion and fission are directly involved in cell energetics (342). Fusion produces a connected mitochondrial network that participates in the maintenance of SMC homeostasis (low level of O_2^- and H_2O_2) (132). Mitofusion depends on mitofusin 2 present on the external membrane of mitochondria, but mitofusin overexpression also activates SMC apoptosis (196). In contrast, the fragmentation of mitochondria (mitofission) in response to stress enhances mitophagy and mitochondrial renewal. Mitofission is dependent on GTPase activities, associated with a high level of ROS release and a shift from glycolysis to fatty acid oxidation. Mitofission is necessary for SMC migration and proliferation (564).

In parallel, submembranous NOX, which promotes the reduction of O_2 to superoxide anion ($NADPH \rightarrow NADP^+ + H^+ + O_2^-$), is constitutively active in SMCs. Its physiological role is to regenerate NADP (electron acceptor) as a coenzyme of the cytosolic pentose phosphate pathway, which is directly involved in cholesterol and fatty acid biosynthesis, nucleotide and DNA synthesis, and reduction in glutathione. NADP also participates in cytosolic glycolysis and calcium mobilization. NAD can be converted to NADP and back to NAD via kinase (314) and phosphatase activities. In this metabolic context, NOX permanently participates in the cytoplasmic redox state and responds to mechanotransduction, allowing the biosynthesis of cell component, and cell adaptation to mechanical forces (63). As seen above, SMC tensegrity, contraction/relaxation, migratory capacity, and phagocytic ability all involve actin dynamics, regulated by the redox state of the cell (468).

H. Nuclear Mechanotransduction

The impacts of tensile mechanotransduction in the arterial wall are not limited to the ECM, the SMC cytoskeleton, and GPCR but also involve nuclear structure and function. With regard to the other cell compartments, depending on the microenvironment, the nucleus is a target for structural and functional reshaping (360). Inner and outer membranes (nuclear envelop) fenestrated by nuclear pores with encapsulating lamins (intermediary filaments) enclose the nuclear compartment. Chromatin (DNA+histones) can be transcription-silenced, tightly packaged in heterochromatin, and linked to lamin, whereas transcriptionally active chromatin is loosely compacted in euchromatin in the nucleolus. The bidirectional shift between hetero- and euchromatin is

dependent on mechanotransduction, regulating the epigenetic control of gene expression (223). In this context, nuclear G-actin, a transcription cofactor, decreases because of its consumption by nuclear F-actin polymerization, leading to attenuation of transcription and trimethylation of histone H3 in stem cells (299). Chromatin is also a direct rheological target, structurally able to move from compaction to elongation (opening) and to resist stretching by plasticity (248).

The first observations suggesting that there are mechanical relations between ECM, cells, and cell nuclei were reported in the 1980s and 1990s (207, 245). The nuclear envelope is mechanically coupled to cell stretching via the molecular linkers of the nucleoskeleton to the cytoskeleton (LINC) (250, 565). It has been shown that the mechanical environment of vascular SMCs impacts the state of their chromatin, thereby controlling vascular gene expression and functions (97). This mechanical nuclear impact depends on the expression, localization, and phosphorylation of the LINC molecular components (Nesprins, Sun proteins, *p*-Emerin, lamins). F-actin clustering in a perinuclear ring and actin-myosin-emerin complex formation are essential in the nuclear transmission of the forces of extrinsic stretching (299). In response to stretching, actin and actomyosin organize an apical perinuclear actin cable connected to basal focal adhesions at the periphery of the cell, increasing the perinuclear tensegrity, forming a cap surrounding the nucleus, limiting the nuclear flattening and reshaping (272). Both myosin activation in the cytoskeleton, and lamin interactions (LINC) in the nuclear envelope, are necessary to ensure this nuclear morphological protection in response to cell strain and deformation.

In this context, the Hippo pathway (MST1/2 kinases, SAV1, MOB1, and LATS1/2 kinases) (316), YAP, and TAZ paralog genes and proteins (413) function as a universal mechanotransduction shuttle between the cytoplasm (phosphorylation and inactivation), inducing cytoplasmic retention and degradation regulated by the actin cytoskeleton (479), and the nucleus. After nuclear translocation, YAP and TAZ serve as transcriptional coregulators, binding enhancer elements forming complexes with TEADs, a family of DNA-binding transcription factors that cannot induce target gene transcription on their own but depend on cofactors (602). A paucity of adhesion, high cell confluency, and a soft adhesion matrix limit YAP and TAZ in the cytoplasm. Conversely, cell contact, strong adhesion to a stiff matrix, and cell stretching and velocity vector dispersion induce YAP and TAZ nuclear translocation and activation of the expression of target genes. Rho GTPases are also involved in this pathway.

Cajal bodies are subnuclear structures usually identified by the presence of coiled threads and a predominant coilin protein (374). Interactions between coilin, survival motoneuron (SMN) proteins, and small ribonucleoproteins form complexes directly involved in gene transcriptional regulation, splicing, telomerase regeneration, and cellular trafficking (219). In a recent study, Poh et al. (435) demonstrated that mechanical forces applied at a cellular level (in association with FRET technology) dissociate the coilin/SMN complex, and this effect is inhibited by F-actin disruption, myosin II antagonism, and lamin A/C suppression. Therefore, these results demonstrate that mechanotransduction can regulate the spliceosomal machinery (shift in isoforms) and, potentially, telomerase activities (220).

Mechanotransduction involving integrins and/or cadherin and GPCR, maintenance of cytoskeletal and nucleoskeletal architecture, and functional responses, including downstream signaling molecular pathways (194, 444)), is energy consumptive. In this context, AMP-activated serine/threonine kinase (AMPK) is a key regulator of energy metabolism (40), including GTP and ATP mitochondrial production and consumption (myosin, actin stress fibers), in association with glucose entry and cytosolic metabolism in SMCs as a second energy source (468).

IV. EVOLUTIVE AND DYNAMIC TELEONOMY OF THE CIRCULATION

Intuitively, the teleonomy of evolution in the animal kingdom, including humans, is the development of specific organ functions, interrelated with a complementary and additive rationalization at the level of the whole organism. This process resembles Taylorism (528), which, applied to living organisms, includes the dividing up and the hierarchy of structures, functions, and their controls. In this context, the dynamic teleonomy of the evolution of animal species appears as a fantastic biological effort to accommodate and/or to escape from, at least partly, the universal compelling natural laws such as, for instance, gravitational forces in terrestrial physics (49, 457) or thermodynamic laws in chemistry (417). This can be achieved only by introducing servo-controlled fueling (energy, metabolic supports) in the biological dynamics of evolution. This servo-controlled fueling is not only necessary for the activation of biological processes but also for the stable maintenance of these basic processes with controlled feedback (for instance, in SMCs, basic internal tension in physiology and dynamic activation of actomyosin sliding, leading to active contraction and active relaxation feedback).

The dynamic teleonomy of the evolving circulatory system, including genetic selection and phenotypic adaptation, involving peripheral resistance to flow and the acquisition of high blood pressure in the peripheral arterial system, is objectively to optimize specific metabolic support for each tissue and organ territory, driven by localized and function-specific active vasodilation. As described above, active vasodilation can only be achieved

by the localized release of basal arterial tone (peripheral resistances, frictional forces) in response to localized functional activities and to their specific metabolic demands. Like active peripheral SMC tone, active vasodilation is also energy consumptive (for instance, G-kinase activation and GTP consumption).

If one agrees with this paradigm, the different evolutive steps of the circulation become explicit:

- diverse archaic hearts as beating muscular tubes propel interstitial flow in open circulatory systems of invertebrates (502);
- "in-series" closed circulatory system in fish involving heart, gills, and periphery (260);
- evolutive heart septation leading to an "in-parallel" divided cardiopulmonary system and the progressive elevation of arterial pressure in tetrapods, amphibians, reptiles, and finally birds and mammals (145);
- the concomitant progressive apparition of numerous branch points in the conductance arteries, distributing blood-borne metabolic support to the functional territories;
- the generation of arterial tone in the resistance arteries, offering the ability to locally relax and dilate;
- and concomitantly the maintenance of diffuse peripheral frictional forces defining high arterial pressure in interaction with the ability of the heart to adapt to high afterload in mammals.

This paradigm covers all the aspects of both the structure and function of arteries, engages bidirectional crosstalk between blood hemodynamics (the content) and the arterial wall (the container), and finally engages arterial SMC plasticity as a survival necessity, actively participating in dynamic arterial structure and function. However, it is also the most common denominator of cardiovascular pathologies (the energetic price to pay).

V. PHYSIOLOGICAL FOOTPRINTS

Compared with fishes, in which flow is highly predominant without important pressure, arterial hemodynamics in adult mammals involve both flow and pressure, with permanent systemic or localized energy transfer between the two and dissipation of both

A. Energy Conservation, Transfer, and Dissipation

The blood is a viscous fluid, with predominant mechanical energy transfer and small dissipation in conductance arteries, whereas mechanical energy is mainly dissipated through frictional forces in distal resistance arteries leading to low velocity and pressure in the capillaries **(FIGURE 8)**.

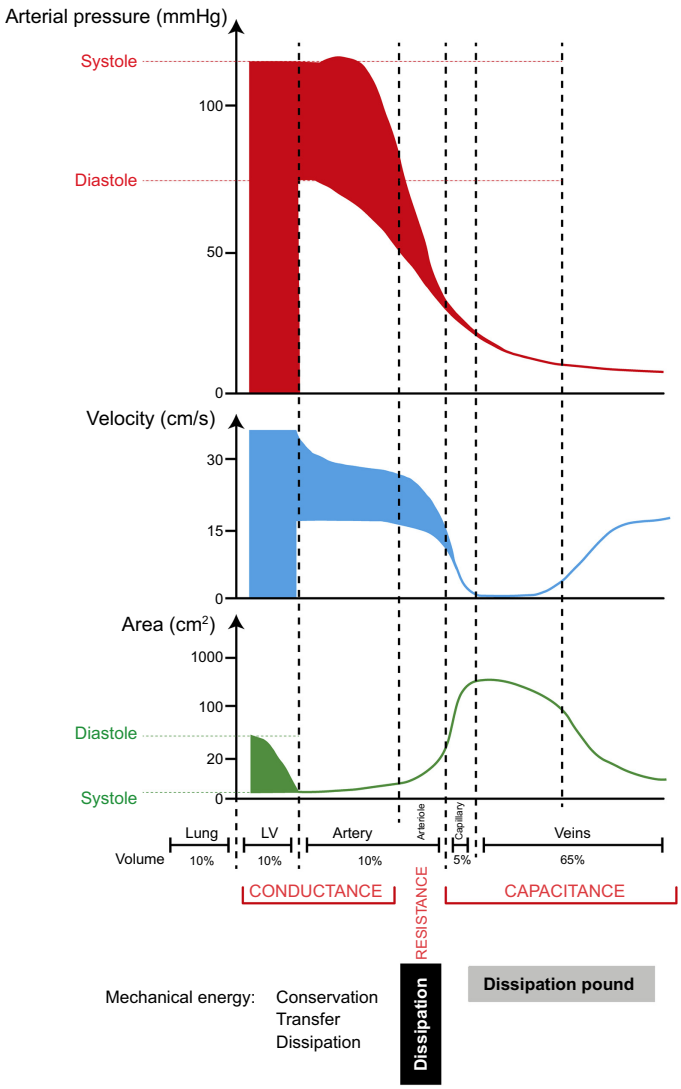

FIGURE 8. Mechanical energetic compartments. Mechanical energetics in the arterial system are complex, involving conservation, transfer, dissipation, and heat production in the different sectors of the arterial system, including the left ventricle. The mechanical efficiency of the arterial circulation is never 100% and depends on changes in arterial wall geometry (tapering and bifurcations, stenosis and dilation) and hemodynamics (pulsatility of flow and pressure versus cushioning and damping). The left ventricular ejection function is essentially due to energy transfer, and the conductance arteries are the sites of conservation, transfer, and low dissipation. The resistance arteries are predominantly the site of dissipation and cushioning pulsatility. The capillaries and veins are capacitance sites of low mechanical energy with continuous flow, low velocity and low pressure (dissipation pound), with pressure-dependent blood stasis and wall distension (256). The pulmonary circulation, not represented in the graph, is a site of pulsatile flow (Ek), low pressure (low resistance), and relative capacitance due to change in pressure (passive wall distension, and capillary dissipation as water leaks when pressure increases).

B. Outward Radial Conductance of Soluble Mediators (FIGURE 9)

One of the most important interactions between hemodynamics and the arterial wall is the advective outward hy-

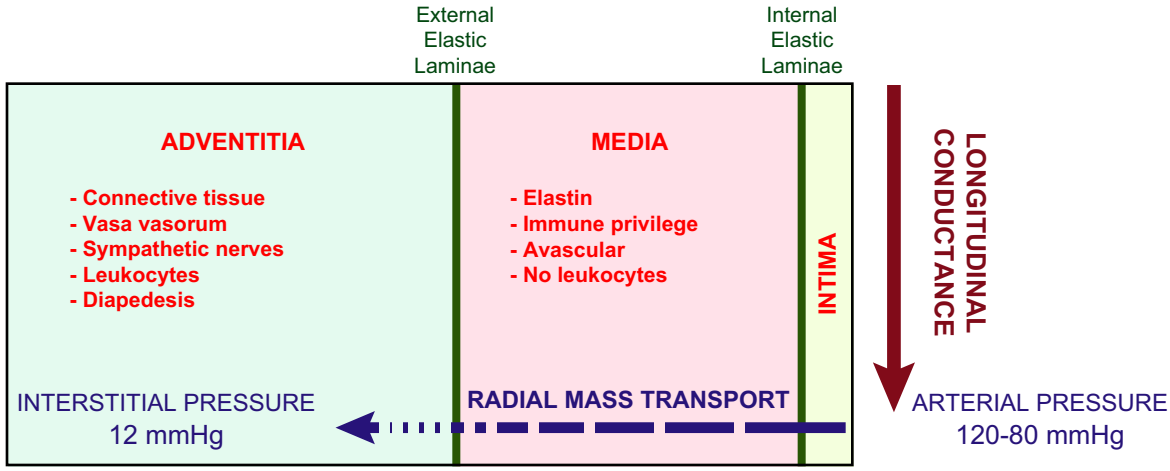

FIGURE 9. Solute convection through the wall. The pressure gradient (100 mmHg) between the arterial lumen and the adventitial interstitial pressure promotes a radial advective conductance of plasma solutes across the arterial wall. This aqueous conductance is small as compared with the longitudinal conductance but conveys almost all the plasma-soluble molecules and microparticles present in the plasma. During this outward transport, the convected molecules can interact or not with the cellular and matrix wall components.

draulic conductance from blood across the wall, a phenomenon defined by the arterial pressure gradient and wall permeability (88). This phenomenon obeys Newton's law of motion (published in 1687 in *Philosophiæ Naturalis Principia Mathematica*) and Bernoulli's principle of fluid dynamics (published in 1738 in *Hydrodynamica*): the pressure gradient force determines unidirectional hydraulic conductance from highly pressurized blood (120–80 mmHg) to the adventitial interstitium of low pressure (<15 mmHg). This radial conductance is the main determinant of the unidirectional mass transport through the arterial wall (outward convection). In contrast, diffusion is the main determinant of transmural transport in fish, in the mammalian fetus, and in venous and capillary systems after birth. In this arterial paradigm, the soluble components present in plasma or generated at the blood/wall interface or in the intima or media, outwardly percolate through the wall layers, including first the endothelial barrier, then the media, and finally the adventitia, in which the transported molecular components can be recycled by the adventitial vasa vasorum and lymphatics by passage into the general circulation. Flow and shear stress also directly impact mass transport through the wall: high shear rate limits mass transport by a washing effect, whereas low shear and oscillatory flow promote the outward convection of plasma components (87).

The first description of this percolation of plasma components through the arterial wall was made by Nikolai Anitschkow more than 100 years ago (15), who described the pressure-dependent exfiltration of plasma lipid transporters towards and retention within the arterial wall in the context of atherosclerosis (see below). Wilens confirmed this paradigm by showing that this radial mass transport is specific of the arterial part of the circulation (absent in veins and low in the pulmonary artery), thus depending on arterial pressure and wall permeability (576, 578). Convection of the soluble and microparticulate components of the blood through the wall reflects the hemodynamic energy dissipation within the wall, systemically defined by arterial blood pressure, but locally modified by specific hemodynamics and structure and function of the wall. As compared with the longitudinal flow (5 L/min), the convected transmural flow is extremely low but constantly exists throughout the life, and can vary in relation to arterial wall heterogeneities, and their impact on vasomotor functions and geometries (386). These data were expanded to tracers other than lipids, particularly using radioactive plasma albumin (89). This approach allowed to decipher the circulating and wall parameters involved in radial transport through the wall (88).

This radial transport is potentially involved in the physiological absence of any microcirculatory vessels within the medial tissue because of the radial transport from plasma of ionized oxygen, glucose [involving the glucose transporter 10 (GLUT10) at the SMC membrane (519)], and other substances. Outward convection is physiologically sufficient to support the metabolic needs of the media, and there is no evolutive necessity for the presence of intramural capillaries except in the external part of the thoracic aorta (583). Therefore, radial advective transport becomes a survival necessity for the arterial media in mammals in response to metabolic needs generated by tensegrity and contractile tone of SMCs. In contrast, diffusion is sufficient for the not yet pressurized arterial wall during fetal life and in the venous and pulmonary artery walls after birth. Thus any postnatal inward intrusion of vessels, due to neoangiogenesis, from the adventitia (vasa vasorum) to the media and the intima within the arterial wall is not physiological but is associated with arterial pathology.

In the same way, outwardly convected serum (S) components have been identified as trophic factors for cultured SMCs (459) via SRF and serum responsive element (SRE) associated with myocardin. Since serum is the supernatant obtained after blood clotting, it includes numerous molecules such as growth factors derived from circulating cells, mainly platelets, whereas the most aggressive proteolytic enzymes and oxidases are blocked by their corresponding plasma inhibitors. Plasma alone is certainly less rich in trophic factors than serum but nevertheless does contain them. Therefore, permanent advective transport of circulating plasma growth factors through the wall participates in maintaining physiological arterial wall trophicity and function.

Generalized or localized outward mass transport across the arterial wall is dependent on both general and local hemodynamic parameters involving pressure, pulsatility, wall distension, shear stresses, physicochemical characteristics of the conveyed proteins (molecular weight, electrical charge, hydrophilic or hydrophobic properties), and local wall porosity. Endothelial integrity is the first mechanical barrier to outward mass transport through the wall due to tight and adherent junctions between endothelial cells (41, 169, 265, 529). In the same way, relaxation and contraction of SMCs, corresponding to both compaction and dilation of the wall tissue, are important determinants of permeability and outward mass transport (SMC relaxation increases medial permeability, whereas SMC contraction decreases it) (88, 100, 341). Other structural components of the wall are also important, such as integrity of the elastic network (439). Laminar flow limits radial mass transport (87) via a mechanical washing effect, and conversely, endothelial NO synthesis promotes subjacent SMC relaxation and potentially increases medial permeability. Inversely, oscillatory flow, transverse wall shear stress (424), velocity vector dispersion due to changes in arterial wall geometry (bifurcations), fixed points in vortices (23), flow impingement and the dissipation of energy within the arterial wall, all locally promote mass transport.

In addition to its role as a mechanical barrier, the endothelium also plays a role as a biochemical barrier, in particular for small peptides, due to its enrichment in peptidases such as angiotensin converting enzyme (ACE) or neutral endopeptidase (NEP; neprilysin, able to degrade natriuretic peptides, NPs) (496), endothelin converting enzyme (ECE), aminopeptidases, etc. but also peptide receptors such as the AT1 receptor to angiotensin II (439), the ET_A receptor to endothelin (387), or particulate guanylate cyclase and clearance receptors to NPs also play a role (447). Due to these direct interactions between circulating small peptides and lytic and/or clearance capacities expressed by endothelial cells, the probability of peptide passage towards the mural SMCs through the endothelium is low. For instance, several years ago, using tissue, plasma, and urine cGMP as in vivo markers of guanylate cyclase activities involving both particulate guanylate cyclase (sensitive NPs) and/or soluble guanylate cyclase (sensitive to NO), we demonstrated that high levels of circulating NP directly impact the production of cGMP by the endothelium and its release into plasma and urine but have no effect on cGMP concentrations in the arterial wall (18, 19). In contrast, NO and soluble guanylate cyclase directly impact cGMP in the medial SMCs (20). These data suggest that the ability of NPs to cross the endothelial barrier is limited by biochemical interactions (proteolysis and clearance).

In this context, the next question is what happens to the plasma solute components when they are outwardly conveyed across the wall? All soluble plasma proteins and macromolecules percolate through the media at a rate dependent on their physicochemical properties. Some of them are neutral and potentially do not interact with the medial components [albumin (90), transthyretin] and can be used for measuring wall permeability. Some are trophic factors, able to cause SMC proliferation at specific localizations where the mass transport is particularly high in relation to hemodynamic load and/or wall permeability, such as bifurcations or injured segments. Other molecules able to interact with the cell or matrix wall components may be retained within the matrix or activated on SMC membranes. For instance, circulating MMP-7 (matrilysin) and MMP-3 (stromelysin) are retained in the alcianophilic ECM mucoid substance (57), whereas plasminogen can be converted into plasmin on the SMC membrane (338) (see sect. VI*D*).

The unmodified or transformed products generated by the blood/wall interactions or released by SMC responses are logically also outwardly convected to the adventitia, where they may initiate new signaling that is able to greatly modify adventitial structure and function, involving inward neoangiogenesis, an immune adaptive response, or fibrosis (see below pathological examples).

In addition to the canonical functions of matrix synthesis and contraction, medial SMCs phylogenetically acquire a high degree of plasticity, developing or reactivating several functions in response to unidirectional radial convection of plasma components, such as endocytosis, phagocytosis, migration and proliferation, acquisition of an osteoblastic phenotype, organization of adventitia, and others. Radial mass transport is a physiological parameter, which permanently maintains SMC plasticity, in part by epigenetic impact in relation to mechanotransduction. This phenomenon becomes crucial in arterial pathologies. By their ability to endocytose transmurally convected elements via scavenger receptors and to phagocytose cellular elements (heterophagy), SMCs acquire clearance functions in the medial layer of the arterial wall (see below).

C. Inward Functional and Structural Cellular Conductance

As described above, the outward convection is unidirectional due to the dissipation of the hemodynamic energy (flow and pressure) within the arterial wall. Thus there is no reverse interstitial fluidic conductance from the adventitia to the lumen. All signaling molecules originating from the adventitia are inwardly transported via the SMC network, passing from cell to cell via the intercellular connexins. For instance, these intercellular communications are the principle means of diffusing the contractile tone signaling generated at the adventitia/media interface by the sympathetic/SMC synapses and inwardly diffusing through the wall SMCs (see sect. III*A*, **FIGURE 4*C***).

In the same way, living vascular SMCs and endothelial cells (ECs) can migrate inwardly (and proliferate) in response to growth factors generated inside and outwardly convected, as an example of living beings circumventing the general mechanical laws by energy fueling (metabolic substrate consumption) **(FIGURE 10)**. This ability of medial SMCs to inwardly migrate and proliferate in the intima in response to platelet-induced or mechanically induced luminal injury was described 40 yr ago (458). Similarly, the ability of adventitial ECs to sprout and penetrate the media as inward neoangiogenesis in response to specific growth factors has been more recently characterized, particularly in References 151 and 378 (see below), but not limited to, the context of atheroma (268).

D. Collision of Blood Particles with the Wall

Any change in wall geometry causes mechanical impingement or stagnation of blood flow, inducing collision of circulating cells with the arterial wall or between themselves. In laminar conditions of flow, the particulate components of blood remain in the central axis of flow, whereas the peripheral position of plasma favors its interface with the wall. In contrast, any changes in geometry induce loss of laminarity, microscopic dispersion and heterogeneity of particle velocity vectors, and an increase in internal energy (entropy) of the particulate part of the blood, facilitating collision with the wall. Collisions of blood cells with the wall are mainly due to the angulation of bifurcations or the presence of luminal narrowing but also depend on the hemorheology of the circulating cells **(FIGURE 10)**. Collision of blood cells between themselves is mainly due to functional or structural luminal dilations (aneurysms, poststenotic dilation, anatomical sinuses, etc.) associated with blood stagnation and vortices.

RBCs and platelets are the most abundant circulating cells and therefore represent the main blood particulate elements colliding with the arterial wall in regions where biomechanical stress drives the formation of intimal tears and of small intimal hematomas. In a laminar rheological environment, since RBCs concentrate in the core of the stream, platelets are expelled towards the periphery, close to the endothelium (1, 174, 543). RBCs (8 μm diameter) are highly deformable, allowing them to penetrate very small channels, such as the 0.5-μm-wide endothelial slits in the spleen, and adapt their form to the circulating shear rate (550). This property is lost when the flow

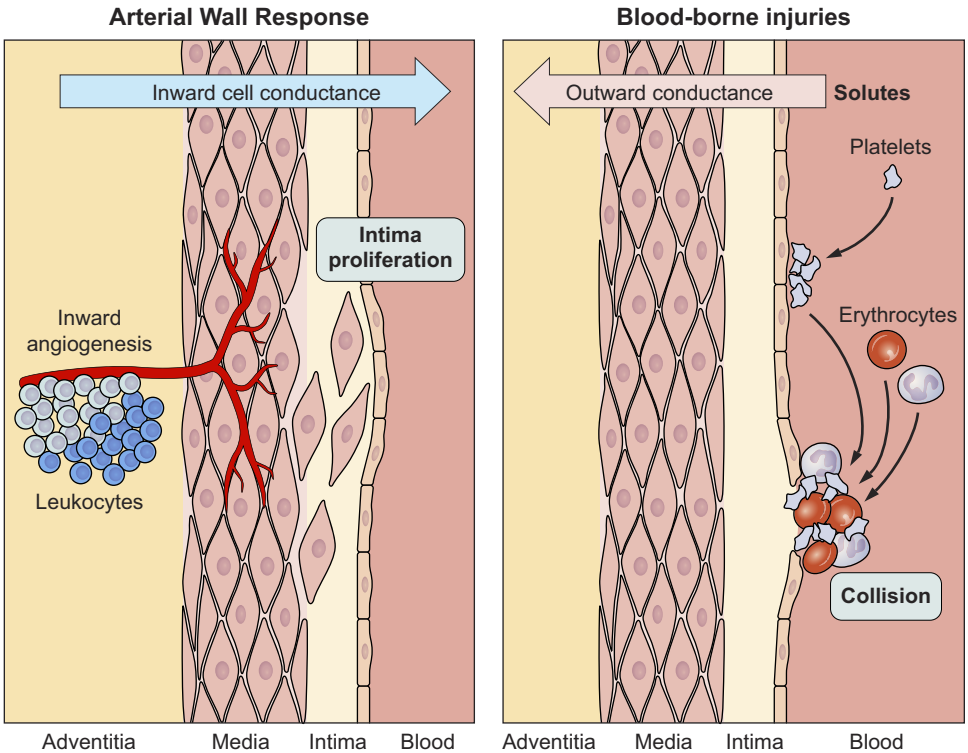

FIGURE 10. Cellular conductance. Outward convection is unidirectional from inside to outside the arterial wall. Conversely, interstitial retrodiffusion of solutes from the adventitia to the inner wall does not occur. The arterial wall usually responds to the outward interstitial mass transport by cellular conductance, involving inward migration and proliferation of smooth muscle cells from media to intima (repair) and endothelial cell sprouting from the adventitia towards the media forming neo-angiogenesis. Due to its connective tissue nature, the adventitia is a capillary- and postcapillary venule-rich structure and a privileged site for leukocyte diapedesis, including lymphocytes able to promote tertiary lymphocyte organs able to locally mature adaptive immunity.

becomes nonlaminar. Collision of RBCs with the wall is potentially a major cause of oxidation since RBCs release hemoglobin and redox-active ferrous (Fe^{2+}) iron, the main catalyzer of oxidation (Fenton reaction). Collision of platelets with the vessel wall in areas of de-endothelialization or loosened endothelial junctions leads to interactions between platelets and the subendothelial matrix (600). These interactions can cause platelet activation and aggregation, which induce the release of numerous mediators contained in platelet granules, including growth factors (PDGF, TGF-β), antiproteases (61), chemokines, and immunomodulatory factors. In particular, activated and aggregated platelets are sites of interaction with neutrophils. Thus, in addition to being sources of cholesterol via their cholesterol-rich membrane, RBCs and platelets promote oxidation and remodeling within the arterial wall. In contrast, the probability of collision of leukocytes with the wall is less frequent because there are less leukocytes in blood (100-fold less numerous than platelets and 1,000-fold less than RBCs). In particular, the rolling of leukocytes on the endothelium of conductance arteries is limited by the shear stress, and adhesion and diapedesis within tissues are highly specific to the microcirculation, mainly the postcapillary venules, with a specific endothelial phenotype (high endothelial venules, HEV), which is only physiologically present in the adventitia of arteries (489) and in inward neoangiogenesis in pathologies.

E. Epigenetic Plasticity of Vascular SMCs (FIGURE 11)

Epigenetic regulation involves a set of molecular mechanisms that control the expression of genes in a cell and in tissues, leading to particularities specifically adapted to functions. Epigenetics control a large part of the development (450) from undifferentiated initial stem cells to differentiated cells and tissue specification in embryonic, fetal life, and during postnatal growth (13). Epigenetic memory involves the inheritances of acquired phenotypic traits via mitosis, which transmits the chromatin, containing DNA sequences together with their own histone enzymatic and electrostatic microenvironment which has undergone epigenetic modifications. The orchestration of gene expression in a tissue-, cell-, and time-dependent manner is the fact of invariant chromatin domains which spatially foster enhancers/promoters interaction (topologically associating domains, TAD) through DNA loop extrusion by cohesion complex and zinc finger (loop extruding factor) and topological insulation (55). All the forces, including mechanotransduction, that shape the chromatin impact these regulations. These modifications involve both histones and DNA, including histone acetylation, which usually increases DNA accessibility to transcription factors, methylation of DNA, which usually represses expression, and noncoding RNAs (miRNA, lncRNA), which can compete with coding RNAs or greatly reduce their half-life. These modifications of a gene's epi-microenvironment can, in some cases, be reversible. For instance, acetylation of histones under the control of histone acetyl transferase complexes (HAT) can be reversible under the effects of histone deacetylases (HDACs), such as those of the sirtuin family (448) (see below).

In relation to outward soluble mass transport, circulating cell collision, and diverse (mechanical, oxidative, proteolytic, etc.) wall injuries, SMCs are able to adapt by shifting from canonical contractile phenotype to more diverse phe-

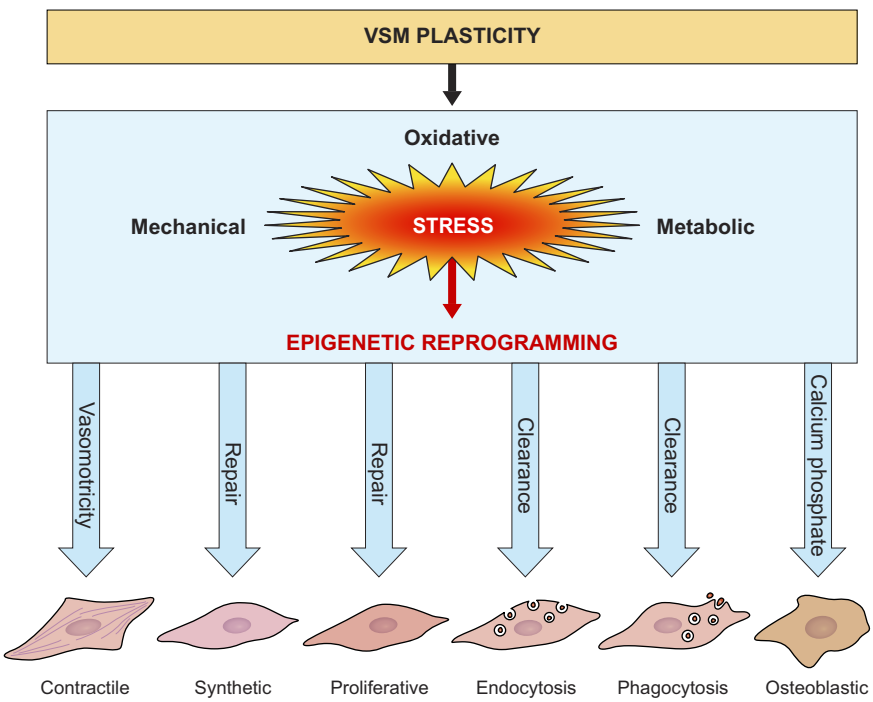

FIGURE 11. Smooth muscle cell (SMC) epigenetic plasticity. In response to blood-borne injuries, SMC can constitutively modify their pattern of gene expression, and in this way to acquire new phenotypes. VSM, vascular smooth muscle.

notypes (393). Over the last 30 years, the shift from a contractile to a proliferative and synthetic phenotype has been the most studied involving SRF/myocardin interactions with CArG boxes on the promoters of genes coding for SMC contractile proteins (SM22a, MYH-11, calponin, etc.) on one hand and the partial limitation of this pathway by an epigenetic complex associating HDAC2, KLF4, and p-ELK on the G/C repressor of these genes in response to injury on the other hand (467). The molecular mechanisms of other phenotypic shifts [endocytosis of lipids and foam cell formation, clearance of protease/antiprotease complexes, phagocytosis, osteoblastic phenotype (234, 303)] and their interactions with canonical SMC processes (contractile/synthetic) open up a new field of research. These shifts are adaptations to changing environmental conditions and are potentially due to an adaptive waking up of archaic functions through epigenetic memory, as described above for the myoepithelioid shift of SMCs in the glomerular afferent arterioles under renin stimulation conditions (326). This plasticity renders the identification of the SMC lineage within the arterial wall particularly difficult during functional changes. For instance, the waking up of endocytotic and phagocytotic functions related or not with clearance activities is associated with the expression of the phagolysosomal CD68 antigen, which was initially described in the transition of circulating monocytes of myeloid origin to tissue macrophages, conferring upon the SMCs a macrophage-like phenotype (455). This led to the misinterpretation of the SMC phenotypic shift as an intrusion of macrophages into the arterial wall. It was thus necessary to develop new specific epigenetic markers of cell lineage rather than functional markers (CD68) of the phenotypic switch. This observation provides also evidence of common functional memories for adaptation to change in environmental conditions (endocytosis and phagocytosis here) whatever the cell lineages.

Arterial SMCs acquire specific epigenetic footprints during development (180). Since SMCs are not terminally differentiated and easily partially or totally reverse their contractile phenotype, it is important to define a marker of SMC identity through lineage memory. A specific epigenetic mark has been recently identified by associating in situ hybridization and a proximity ligation assay between H3K4me2 at the locus of SMC myosin, which is restricted to the SMC lineage (179) regardless of the phenotype switch.

Epigenetics encompasses different molecular processes, which lead to phenotypic heritability that does not depend on changes in DNA sequences involved in the inheritance of genetic traits. Therefore, epigenetic adaptive or mismatching memory differs from genetic inheritance but also from the canonical response (ligand receptors, second messengers, nuclear translocation, gene expression) to reversible changes in environmental conditions. For instance, specific cellular differentiation in a Taylorized and hierarchized organism is a broad area of epigenetic applications (450). These epigenetic processes encompass DNA methylation on CpG sites (252); histone (H) modifications, mainly acetylation or methylation on lysine (K) or arginine (R) residues; phosphorylation and ubiquitination (189); and long (lnc) (324) or micro (mi) noncoding interfering RNA (544). Methylation of C in CpG sites in the promoter region of a gene (particularly housekeeping genes) silences gene expression. Acetylation of the histone NH_2-terminal tail diminishes the electrostatic affinity between histone proteins and DNA and thereby promotes a chromatin structure that is more permissive to gene transcription. This process is under the control of enzymes: methylase, HAT, and HDAC. The binding of noncoding RNAs to their mRNA target through base pairing leads to mRNA degradation when pairing is complete or inhibition of translation when pairing is partial. Several miRNAs can bind the same mRNA, and a single miRNA can bind several mRNAs, showing the complexity of the noncoding RNA system in the regulation of gene expression. Noncoding interfering RNAs can be transported in cell-generated exosomes (601) and, therefore, may be detected in blood as peripheral biomarkers (54).

Since the specific maturation of arterial wall structure takes place during fetal life and postnatal development, and since arterial pressure remains low during fetal life, it is clear that high arterial pressure does not directly drive the ontogeny of arterial wall modeling. Conversely, vascular SMC differentiation appears early in mouse development and is common to arteries and veins (304). This specific modeling involves the three-layered structuring of the wall, supported by flow-dependent endothelial propagation, as the initial driving force for initiation of tube formation and recruitment of mural cells through endothelial PDGF (451) and basic fibroblast growth factor (16) expression and secretion during fetal life in the absence of high pressure. Therefore, arterial wall structuring during fetal life is potentially an exaptation to adapt SMCs and ECM to arterial tensile stress after birth. The arterial wall is not completely matured by flow at birth because of the low level of pressure, the second fundamental and more recent hemodynamic stimulus. Therefore, postnatal pressure-dependent stretching (mechanotransduction) of the arterial wall potentially exerts a dynamic epigenetic control of the SMC phenotype during growth, which continues throughout life. The numerous epigenetic mechanisms involved in postnatal adaptation to the Laplace law remain to be deciphered.

VI. FROM CIRCULATORY EVOLUTION TO CARDIOVASCULAR PATHOLOGIES

In this last section we will try to show through examples how the phylogenesis of the circulation and its physiological footprints (mechanical energy transfer or dissipation, mechanotransduction, outward convection, inward cellular

conductances, circulating cell collision, and epigenetic plasticity of SMCs) are the most common denominators of human cardiovascular pathologies involved in both the damage and the responses of the arterial wall.

A. Atheroma

Due to the immeasurable number of scientific and medical publications on atheroma, atherosclerosis, or atherothrombosis, this article does not intend to be an exhaustive review of the disease, which, however, remains the first cause of death in developed countries. We will focus on the hemodynamic consequences and the roles of the SMCs in the different stages of human atheroma progression. Seymour Glagov (1925–2008) was a pioneer in observing (autopsies) and establishing (primate experiments, biophysical approaches) a direct relationship between privileged sites of atherothrombotic development (internal carotid artery, infrarenal abdominal aorta, and coronary arteries) and hemodynamic stress (170, 171), including low shear stress, oscillatory shear stress (38, 39, 287), and high tensile stress (581).

1. Fatty streaks

The initial stage of atheroma is the subendothelial accumulation of yellow lipids named "fatty streaks" in the highly pressurized arterial part of the circulation, both in animals (15) and humans (391). The low pressurized veins and pulmonary artery are devoid of fatty streaks, showing that arterial pressure-dependent unidirectional advective convection of lipid plasma transporters is a necessary condition for the development of fatty streaks **(FIGURE 9)**. Fatty streaks are related to both the outward transport of lipids by lipoproteins from the plasma through the wall and the specific retention due to interaction of low-density lipoprotein (LDL) with glycosaminoglycans (GAG) (520) synthesized and secreted by intimal SMCs. The interactions of apolipoproteins with highly sulfated, negatively charged GAGs are mainly due to the positively charged domains of apo B100 (lysine and arginine-rich domains), both in experimental animals [rabbit (437) and mouse (491)] and in humans (83, 597) **(FIGURE 12)**.

Circulating high-density lipoproteins (HDLs) are also convected through the wall but not retained as are LDLs. But $apoA_1$ can be oxidized during this mass transport, inducing dissociation of $apoA_1$ from its lipid cargo (121, 239). Free oxidized $apoA_1$ (molecular mass 25–30 kDa) and A_2 are rapidly filtrated and metabolized in the proximal tubule, involving cubulin/megalin-dependent endocytosis by epithelial cells (127, 210, 283, 366) responsible for the observed decrease in circulating HDL. Inversion of the diet from cholesterol-rich to cholesterol-poor is able to reverse the lesions in rabbit (535). It is interesting to note that, except for the rabbit, the majority of mammals do not spontaneously develop atheroma in response to a high-fat diet but instead develop hepatic steatosis (592). This is due to their lipid-poor regimen in wild life, the totally different lipid transporter profiles (596) in animals relative to those in humans, and the nature of the proteoglycans synthesized by SMCs. Zebrafishes develop some lipid deposits in the dorsal aorta under the endothelium, associated with increases in endothelial permeability, predominantly at bifurcations, when subjected to a high-cholesterol diet (504). However, these lesions remain limited to deposits in the absence of an arterial wall medial layer and low outward mass transport. Therefore, the zebrafish model appears to be more adapted for studying lipid metabolism and oxidative stress (143). Some arteriosclerosis has been described in salmon (147). These lesions develop in the proximal part of the salmon coronary artery, which is externally mechani-

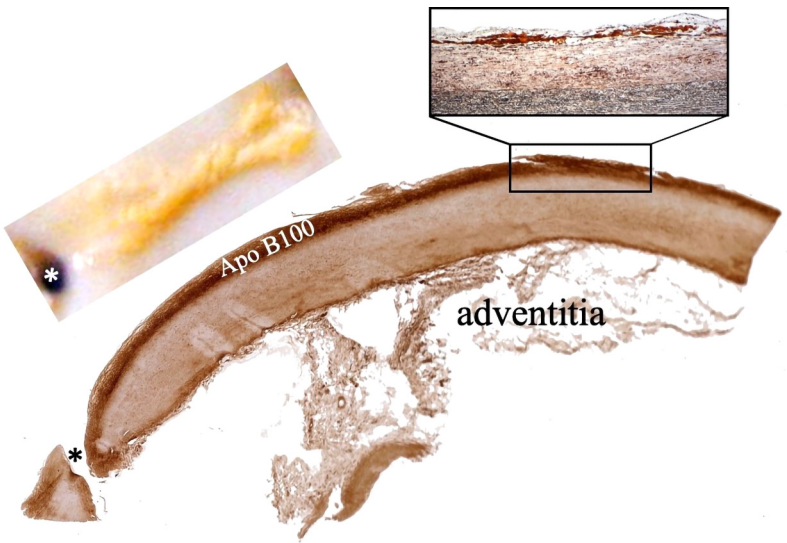

FIGURE 12. Macroscopic and histological (apo B100 immunostaining) views of human aortic intimal fatty streaks in close contact with intercostal ostia (*). The abundance of apo B staining provides evidences of *1*) the outward convection of low-density lipoprotein (LDL) from plasma and *2*) the interaction and retention of LDL in the intima at the initial stages of human atheroma.

cally injured by the beating conus arteriosus. There are no lipid deposits in the wall, only endo-proliferation of SMCs and endofibrosis. Such an impact of external repeated motion (external mechanical fatigue of the wall) also has been described in humans, such as in iliac artery endofibrosis in cyclists (158). Likewise, arteriosclerosis was observed in elephants involving medial fibrosis, arterial dilation and calcifications (335), related to age but not to lipids (336).

In humans, bifurcation rheology favors fatty streak development, including the posterior intercostal ostia in the aorta **(FIGURE 12)**, and on an SMC background. These preferential localizations are dependent on local hemodynamic, including low shear, flow oscillation and recirculation, flow impingement, corresponding finally to dissipation of mechanical (Ep and Ek) energy within the wall. At this stage, part of the cholesterol can be engulfed, forming foam cells. SMCs are able to endocytose LDL, to partly metabolize cholesterol (308, 309, 412), and to form liquid and solid cholesterol crystals (228). Induction of fatty streaks by a cholesterol-rich diet in primates can be reversed by diet inversion (605), and a relationship of lesion regression to wasting diseases was proposed after comparing undernourished and obese subjects in an autopsy series (577). The endocytosis capacities of SMCs are not limited to modified LDL but also include the clearance of protease/antiprotease complexes, in which plasma zymogens are activated on SMCs and form complexes with tissue antiproteases, and the complexes can be cleared by endocytosis involving LRP-1 scavenger receptors present on SMCs (58).

In this context, the principle of outward convection of plasma components is not limited to LDL but concerns all plasma lipid transporters and circulating zymogens or substrates that can be activated during their advective transport by interactions with SMCs or ECM. For instance, blood-borne complement components are largely present in early plaques, where they can be activated by cholesterol crystals (325).

2. Fibroatheroma

In response to this early lipid injury, the medial SMCs inwardly migrate and undergo subendothelial proliferation, acquiring a proliferative and ECM-synthesizing phenotype, forming a fibrocellular cap, covering the lipid accumulation on its luminal side, and creating a lipid core. In fibroatheroma, the lipid core extends on a predominant acellular background, and the cap SMCs are relatively resistant to atheroma.

3. Foam cell

Foam cell formation can be seen in association with fatty streaks and in the shoulder of the lipid core in fibroatheroma. Translucid and electron-dense foam cells are predominantly of SMC origin, as shown earlier by electron microscopy (165, 166) and more recently by molecular imaging (12, 149, 167, 179, 180), but the ability of SMCs to export cholesterol by the ATP-binding cassette transporter A1 towards HDL is limited compared with that of macrophages of myeloid origin (8).

4. Wall-blood cell collisions

In addition to the outward convection of LDL, the collision of circulating cells with the arterial wall also plays an important role in the initiation of atherosclerosis by releasing cholesterol from cell membranes, proteases and oxidative molecules, and finally, free DNA. This paradigm is not new, since the famous Austrian pathologist C. Rokitansky (1804–1878) described the arterial atheromatous process as evolutive intimal blood deposits (453), including advective insudation of plasma proteins (convection) (610) and blood cell deposit on and integration in the intima. These early data fit well with numerous observations that nonocclusive thrombi or clots can be incorporated into the intima, participating in disease progression and involving lipid accumulation and cholesterol crystallization (reviewed in Ref. 474). The initial observations were reported by J. B. Duguid (another human pathologist) in 1946 (128, 129). The probability of interactions between circulating cells and the wall is in part proportional to their respective densities in the blood (see above). Chandler and Hand (95) proposed that platelet membranes are an important source of cholesterol and foam cell formation via phagocytosis of activated platelets, potentially by SMCs, in early atheroma. These data were confirmed by Kruth (286), showing that fibrin obtained from platelet-poor plasma is insufficient for promoting cholesterol accumulation, whereas fibrin obtained from platelet-rich plasma promotes cholesterol accumulation in rabbits. Moreover, this foam cell accumulation is dependent on platelet activation (phosphatidylserine exposition), phagocytosis, and metabolism by SMCs. The role of platelets in the initiation of atheroma was more recently confirmed by Stephen Massberg in mice (329), promoting the activation and migration of SMCs via PDGF release (330). We recently extended these observations to RBC incorporation in the arterial intima (119). Incorporation of senescent (exposed phosphatidylserine) RBCs within the wall promotes their phagocytosis by SMCs (281). RBC membranes are cholesterol-rich, leading to intracellular cholesterol accumulation, whereas hemoglobin leads to oxidation via Fe^{2+} release (Fenton reaction) in early atheroma (119). These data, initially obtained in human aorta, were recently confirmed in human coronary arteries (157). This ability of SMCs to perform phagocytosis (efferocytosis) of dying cells was first reported by Bennett et al. (44) and, once again, depends on exposed phosphatidylserine. The role of circulating cell collision and clot formation within the wall in the initiation of atheroma was also exemplified by the rare cases of atherothrombotic lesions observed in pulmonary arteries. This was pointed out in the seminal work of Arbustini et

al. (17). In this study, pulmonary artery atherothrombotic plaques were observed in human PH, when PH is secondary to thromboembolic events, but not in primary PH. These cholesterol-rich pultaceous lesions involve RBCs, platelets, and phagocytosis and evolve towards a necrotic core. A similar experimental approach was proposed early on in the rabbit (211). Therefore, whatever the cell type (platelets, RBCs, leukocytes), blood cells incorporate the intima of the arterial wall and undergo efferocytosis by SMCs via exposed phosphatidylserines, metabolizing their membrane cholesterol, forming foam cells, promoting cholesterol crystallization, and releasing their contents within the cell. Nevertheless, the efferocytosis capacities of SMCs are potentially limited, and impaired phagocytosis promotes necrotic core formation and plaque evolution towards vulnerability and clinical expression of the disease (279, 280). This is potentially why there is no debridement of the plaque, only a luminal overlay by the fibrocellular cap.

5. Inward neoangiogenesis

Inward neoangiogenesis represents an important step in the evolution of atherothrombotic pathologies towards their clinical expression, through the ability of neoangiogenesis to promote recurrent intraplaque hemorrhages and their consequences on plaque vulnerability (reviewed in Refs. 353, 358).

J. C. Paterson was the first to report observations of neoangiogenesis and capillary ruptures in coronary atherothrombosis (420), but he described neoangiogenesis developing from the luminal surface (419). It is now well established that plaque neoangiogenesis arises from the adventitial vasa vasorum (35, 290, 553, 609), inwardly penetrating the media towards the plaque in response to outwardly convected growth factors (228). In this process, VEGF plays a predominant role by initiating the sprouting of adventitial endothelial cells towards the media, and medial SMCs are major sources of VEGF (579). It was then shown experimentally that inhibiting VEGF could have beneficial effects on atherothrombosis progression (377, 378) in mice. Since VEGF expression is highly sensitive to hypoxia through hypoxia-inducible transcription factor (HIF), this signaling pathway was proposed to be the driver of inward angiogenesis (492). However, inward neoangiogenesis is initiated early in human atheroma in a context in which relative hypoxia is highly improbable (see above convection of oxygen) and was described in apo-$E^{-/-}$ mice with very thin vessel walls and a normal arterial blood pressure (522). Therefore, we proposed that inward neoangiogenesis can be initiated by intimal phospholipid metabolism and the radial transport of metabolites towards medial SMCs, inducing VEGF expression and secretion through the PPAR-γ signaling pathway (227) **(FIGURE 13)**. Inward neoangiogenesis is characterized by the development of arterioles, capillaries, and venules, allowing diapedesis of circulating myeloid cells such as RBCs, neutrophils, lymphocytes, and monocytes within the arterial tissue. The vessels arising from this neoangiogenesis remain partly immature (130) and are highly susceptible to rupture and bleeding (298, 416). In this context, neoangiogenesis and its intraplaque hemorrhagic complications illustrate well both the principle of outward convection of soluble mediators generated within the arterial wall and the capacity of SMCs to respond to this stimulus.

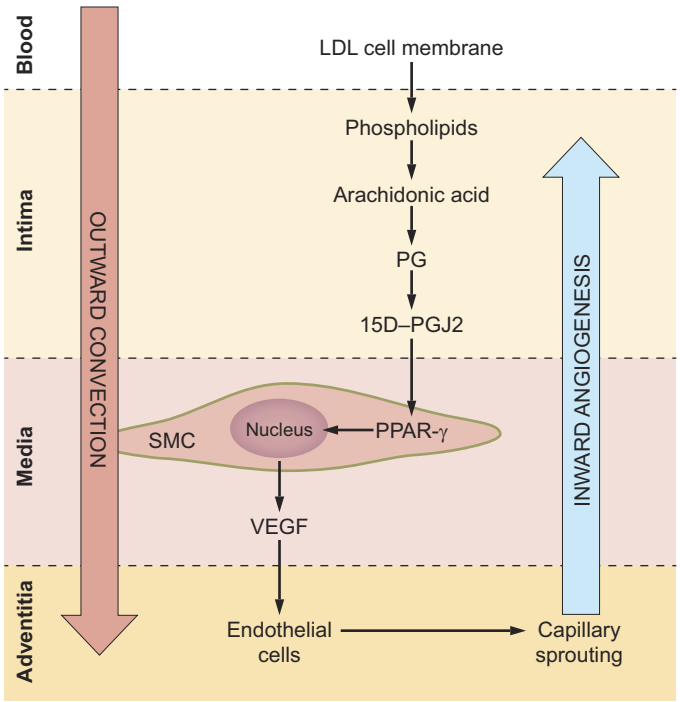

FIGURE 13. Mechanism of inward neoangiogenesis, initiated by the outward transport of phospholipid derivatives (arachidonic pathway) from the plaque to medial smooth muscle cells (SMCs) and the adventitia and accomplished by inward sprouting of endothelial cells from the adventitia towards the plaque. PG, prostaglandin; PPAR, peroxisome proliferator-activated receptor; VEGF, vascular epithelial growth factor.

Finally, neoangiogenesis is the main source of intraplaque hemorrhages, conveying not only highly oxidative RBCs with their cholesterol-rich membranes but also circulating leukocytes of myeloid origin, including neutrophils (351), destined to die and to release highly active proteolytic enzymes (301, 302), platelets, and clot formation-promoting fibrinolytic enzymes (355), potentially participating in fibrous cap degradation and subsequent rupture, and extracellular DNA as a potential substrate for calcium precipitation and hydroxy-apatite nucleation (108). Nevertheless, some cases of plaque rupture can remain silent, and thrombi incorporated into the plaque may cause progression towards a final myocardial infarct (75) or stroke.

6. Erosion

In addition to plaque rupture, another pathophysiological cause of thrombosis, erosion, was observed in an autopsy

series of acute coronary syndrome leading to death (144). Optical coherence tomography and endovascular ultrasound or angioscopy (168, 289) confirmed these initial pathological observations describing a thrombus attached to an intact fibrocellular cap. This phenomenon appears to be relatively specific to acute coronary syndrome and more frequent in women than in men (589). In hemodynamic terms, erosion is related to high frictional forces applied to the endothelium of epicardial coronary plaques and bifurcations due to the diastolic flow entrance, whereas plaque development and rupture are potentially more related to chronic high convection and blood stagnation in epicardial arteries during systole as described above (see sect. III).

B. Adventitial Responses

As shown for neoangiogenesis, the adventitia is a target for arterial wall remodeling, which occurs in different pathologies related to oxidation and proteolysis involving angiogenesis, the adaptive immune response, and fibrosis (357). In contrast to the media, the adventitia is a completely vascularized tissue containing capillaries and venules, which are privileged sites for leukocyte diapedesis, particularly for lymphocytes, mast cells, macrophages, and dendritic cells. It is also a privileged site for the integration of numerous molecular signaling pathways involving outward convection from the lumen and media to the adventitia. Therefore, the adventitia is the main site for the adaptive immune response to arterial wall injury. The usual scenario of this response involves the de novo formation of ectopic adventitial lymphoid granuloma and/or adventitial tertiary lymphoid organs (ATLOs, more complete maturation, B cells) (594), observed in atherothrombosis (595), acquired aneurysm of the abdominal aorta (AAA) (133), autoimmune aortopathy (104), and chronic vascular allograft rejection (533). The development of such a maturing adaptive immune structure, including a germinal center and T helper and B cells, which are able to mature and secrete antibodies, requires both *1*) a network of chemokines and cytokines, adhesion molecules, and crosstalk with tissue stromal cells (193) within the microcirculation; and *2*) neoantigens radially convected from inner lesions to the adventitia. In atherothrombosis (508), including AAA (105), luminal proteins modified by oxidation and/or proteolysis potentially represent the majority of these autoantigens able to support the maturation process towards antibody synthesis and secretion (508). Likewise, some autoimmune diseases, such as lupus erythematosus (161), enhance atherosclerosis progression. In contrast, the autoantigens generated during autoimmune aortopathies remain unknown. In vascular allograft rejection, major histocompatibility complexes (432), generated within the allogenic wall, are directly involved in ATLO formation as demonstrated by their restriction to the allografted segment (532). Whatever the specific immune mechanism and the etiologic context, the constant localization of the adaptive immune responses within the adventitia underlines the constant involvement of the outward convection principle in these phenomena.

Finally, there are some localized specificities in the expression of atherothrombotic pathology: intraplaque hemorrhages in the carotid artery, erosion in the coronary arteries, aneurysm in the abdominal aorta, and osteoid degeneration in the femoral arteries. The relationship of these partial specificities to local hemodynamics has not yet been completely deciphered.

C. Aortic Valve Diseases

Like atheroma, degenerative aortic valve diseases are directly linked to the principle of convection driven by a pressure gradient specific to valve biomechanics (28). The transvalvular pressure gradient peak is diastolic for the aortic valves **(FIGURE 14)**, whereas it is systolic for the mitral valve. Therefore, convection of plasma components through closed aortic valves takes place during diastole, and degenerative pathology always begins and evolves within the fibrosa, the most pressure-exposed layer. Conversely, the pathology always begins in the ventricularis for the mitral valve. As in atheroma, the initial step of the disease is the accumulation of lipids (fatty streaks) in the fibrosa of aortic valves. The role of gravitational force is, once again, exemplified by the aortic valves in giraffes (10). In their study, Amstrup Funder et al. (10) compared the aortic valve in the giraffe and the cow. The giraffe aortic valve is biomechanically 70% stronger and stiffer and morphologically thicker and richer in collagen and elastin compared with that of the cow. These data are only partly reproduced in the mitral valve. This comparison provides evidence of a major role for hemodynamics in cardiac valve structural adaptation and the ensuing degenerative valve disease.

Although arterial atheroma and aortic valve disease share common initial pathways of LDL accumulation in the arterial intima and the valvular fibrosa, these pathologies evolve differently, with a predominant development of calcifications in valves without formation of a true fibrous cap. Promotion of calcifications in soft tissues is always due to ionized calcium precipitation on (inorganic) phosphates, forming calcium-phosphate [$Ca_3(PO_4)_2$] that rapidly organizes into solid hydroxyapatite crystals. The sources of phosphates are numerous, including membranous (438) and transported (lipoproteins) phospholipids (85), metabolism involving phospholipases, energetic metabolism using ATP or GTP as substrates, free DNA (108), and circulating phosphates. Later, the valvular interstitial cells (VICs) can acquire an osteoblastic phenotype (370), thus enhancing the calcification process.

In relation to the convection of plasma lipoproteins through the valve tissue, lipoprotein(a) [LP(a)] plays an original role (399). The epidemiological and genetic data have been con-

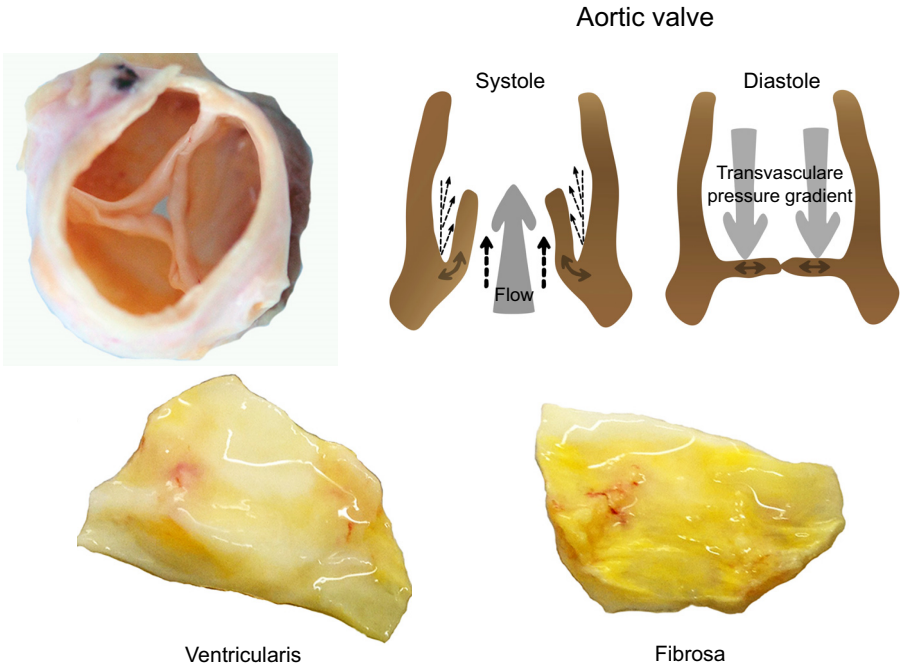

FIGURE 14. Hemodynamics of the aortic valves and the impact of transvalvular convection of lipoproteins during diastole on the initiation of pathology in the fibrosa. Similar convective mechanisms take place in the mitral valve ventricularis during systole (not represented).

firmed in experimental models that are physiologically highly resistant to calcification (mouse, rabbit) (221): the transgenesis of apolipoprotein(a) [apo(a)] in mice or direct intravenous injection of recombinant human apo(a) in rabbits promote the development of aortic valve calcification in these animals (593). LP(a) preferentially transports oxidized phospholipids (45). Apo(a) is a protein that arose during evolution and first appeared in primates from the duplication of the plasminogen gene. Like plasminogen, apo(a) possesses kringle domains (KIV) that are able to bind to the lysine residues in COOH terminals on fibrin but also on proteins of cell membranes, and this binding competes with that of plasminogen (332). In this context, the main ligand of plasminogen on VICs is urokinase (u-PA) retained on the cell membrane by the u-PA receptor (UPAR) (278). A new transmembrane protein able to bind plasminogen has been identified as plasminogen receptor lysine-terminal (PlgRkt) (14). PlgRkt forms clusters with UPAR/u-PA to activate plasminogen. Apo(a) competes with plasminogen on the lysine residue of this receptor (454). Finally, this receptor is involved in the endocytosis and recycling of LP(a) in the liver (484). Therefore, we can reasonably hypothesize that LP(a) could be endocytosed by the VICs via the PlgRkt/u-PAR complex, intracellularly metabolizing its phospholipid cargo and releasing phosphate, which acts as a substrate for calcium precipitation. These points are of importance since lysine mimetics, such as tranexamic acid or ε-aminocaproic acid, are able to inhibit the binding of kringles to COOH-lysine residues, including plasminogen but also apo(a) (497).

Finally, at a more advanced stage of aortic valve disease, as in atherothrombosis, calcifications are associated with the development of neoangiogenesis and peri-calcification bleeding (5, 6). The molecular mechanisms of this neoangiogenesis have not yet been identified. These microbleeds could potentially be related to the von Mises distortion stress (235) between the highly deformable soft viscoelastic tissue part of the valve and the nondeformable rigid/solid calcified inclusion, triggering fatigue-like microscopic tears at the edge of the calcification (267). Nevertheless, neoangiogenesis appears with lipid deposition within the valvular tissue.

Aortic valve stenosis is also a good example of the impact of shear on hemorheology, particularly on vWF and its degradation. vWF is a glycoprotein synthesized and secreted in the plasma by the endothelial cells and the megacariocytes. vWF is secreted as high-molecular-weight (HMW) multimers, able to form one of the initial network of the coagulation by interacting with platelets and provoking their aggregation (233). A defect of vWF function, genetically determined or acquired, promotes hemostatic leakage. Physiologically, vWF is sensitive to shear stress, provoking its elongation and promoting its proteolytic metabolism by ADAMTS13. In pathological conditions of high shear stress, such as aortic stenosis, provoking an important increase in blood velocity, the shear stress is enhanced, increasing the rate of proteolytic degradation of circulating vWF, decreasing its plasma concentration, shifting the HMW multimeric vWF toward low-molecular weight forms, promoting digestive bleedings (551) and potentially mucosa angiodysplasia.

D. Aneurysms

Aneurysms are anatomically defined as localized dilations of the arterial wall, functionally defined as a progressive loss

of the arterial wall's capacity to support its hemodynamic load, and structurally defined as a thinning of the medial layer due to proteolytic degradation of the ECM and SMC loss, leading to rupture regardless of their localization (346). Proteolytic injury of the ECM is usually caused by blood-borne protease/tissue antiprotease imbalance. This imbalance could be extrinsic, related to excess of blood-borne zymogen convection and wall activation, or intrinsic, related to loss of function mutations in the molecular components of the ECM rendering it more sensitive to proteolysis. SMC loss can be also linked to extrinsic or intrinsic pathophysiology. Since adhesion to the ECM is a survival necessity for SMC, proteolytic injury of ECM components could induce SMC apoptosis by detachment (anoikis) (338, 345). Also, as withstanding the constant tensile stress and pulsatile stretching in conductance arteries is energy consumptive for SMCs, genetic or acquired defects in their fueling and corresponding molecular signaling cause SMC loss and progressive wall degradation. Pathological aneurysms can theoretically develop anywhere along the arterial tree, but in fact, they are mainly localized in the abdominal aorta (AAA), the ascending aorta (TAA), and in the intracranial cerebral arteries (ICAs) in humans. Spontaneous aneurysms are rare in the animal kingdom, including in mammals other than humans. Animals appear to be more sensitive to acute rupture (dissections) of the aorta than to progressive dilation (aneurysms). This is particularly true for turkeys (284). The formation of ICAs is also rare in animals (7/2,000 animals including 29 species) (381). AAA formation is mainly due to injury by extrinsic blood-borne components involved in ECM degradation, SMC loss, and the adventitial immune response, whereas TAA formation is more directly or indirectly time-dependent on intrinsic defects in SMCs or ECM function. Understanding the complex and potentially diverse pathophysiology of ICA remains to be explored further.

The clinical and biological pathology of AAA, including its pathophysiology, has been recently extensively reviewed (464). The direct relationship between atherothrombosis in the human infrarenal aorta and acquired AAA development was established by the seminal works of Glagov and coworkers (586, 604), including experimental studies in primates (603). The authors also proposed that the reduced number of lamellar units present in the human infrarenal aorta could sensitize it to AAA development (606). The study of Vollmar et al. (555) potentially confirmed the role of local hemodynamics in the infrarenal aorta, showing that AAAs were more frequent in men with above-knee amputation, and the greater curvature of the aneurysmal sac always developed on the opposite side of the nonamputated leg, suggesting that reflection waves on bifurcations can play an important role in the lateralization of AAAs.

Due to the blood stagnation, flow oscillations, and wave reflections, the infrarenal aorta is a privileged site for blood cell collision and clotting. This initial nonocclusive mural clotting is usually asymptomatic, and blood flow is not greatly perturbated. In this hemodynamic context, blood flow continuously entertains a luminal active process of clotting (540), involving fibrin formation and trapping of all different blood cell types at the interface between circulating blood and the intraluminal thrombus (ILT) usually observed in human AAA (354) **(FIGURE 15)**. Therefore, the ILT is a multilayered biologically dynamic neo-tissue, in which permanent luminal clotting is continuously and progressively counteracted by active fibrinolysis (237) involving several proteases (305), accumulating RBCs and their lysis, which releases their hemoglobin and membranous cholesterol content. Due to the outward convection of numerous proteases and RBC lysis, the biologically active ILT progressively injures the arterial wall by proteolytic and oxidative processes, inducing ECM degradation, SMC loss (354), and adventitial innate and adaptive immune responses (357), finally leading to wall rupture. The pathogenic role of ILT luminal renewal is not only limited to AAA progression but also includes the prevention of the healing process. This is mainly due to the aggressive proteolytic environment (155) and to some related consumption coagulopathies (611), including a decrease in platelet count and plasma fibrinogen concentration, associated with increased D-dimer release but also relative anemia due to RBC retention and lysis in the ILT (327), HDL oxidation, and finally a decrease in the plasma $apoA_1$ concentration (74). Similar processes are at play in chronic dissection of the descending thoracic aorta (465) in relation to blood clot renewal in the false channel.

In contrast, aneurysms of the ascending aorta (TAA) are not related to atherothrombosis, but sometimes fatty streaks and intimal proliferations can be observed, particularly in degenerative form in elderly patients. The ascending aorta is usually devoid of atherosclerosis (581, 604), due to the powerful washing effect of the cardiac systolic ejection. In this context, the rare presence of atheroma could be secondary to the aortopathy (increase in wall permeability). TAAs (except autoimmune Horton's disease, vasculo-Behcet's syndrome, and Takayasu arteritis) are related to three main etiologies: rare hereditary genetic diseases, association with bicuspid aortic valves, and degenerative forms in older patients (recently reviewed in Ref. 352). However, regardless of etiology, mechanotransduction, particularly wall tension (Laplace law) and SMC biology and death, play important roles in the development of TAA and the risk of dissection. Genetic forms involve three families of signaling pathways: mutations in the components of the ECM, in the TGF-β pathways, and in contractile proteins. These three pathways directly implicate different aspects of SMC physiology: adhesion to ECM, protease/antiprotease synthesis and the clearance capacity of SMCs, and finally, contractile function and mechanotransduction, from ECM tensile stress to cytoskeleton and finally nuclear mechanotransduc-

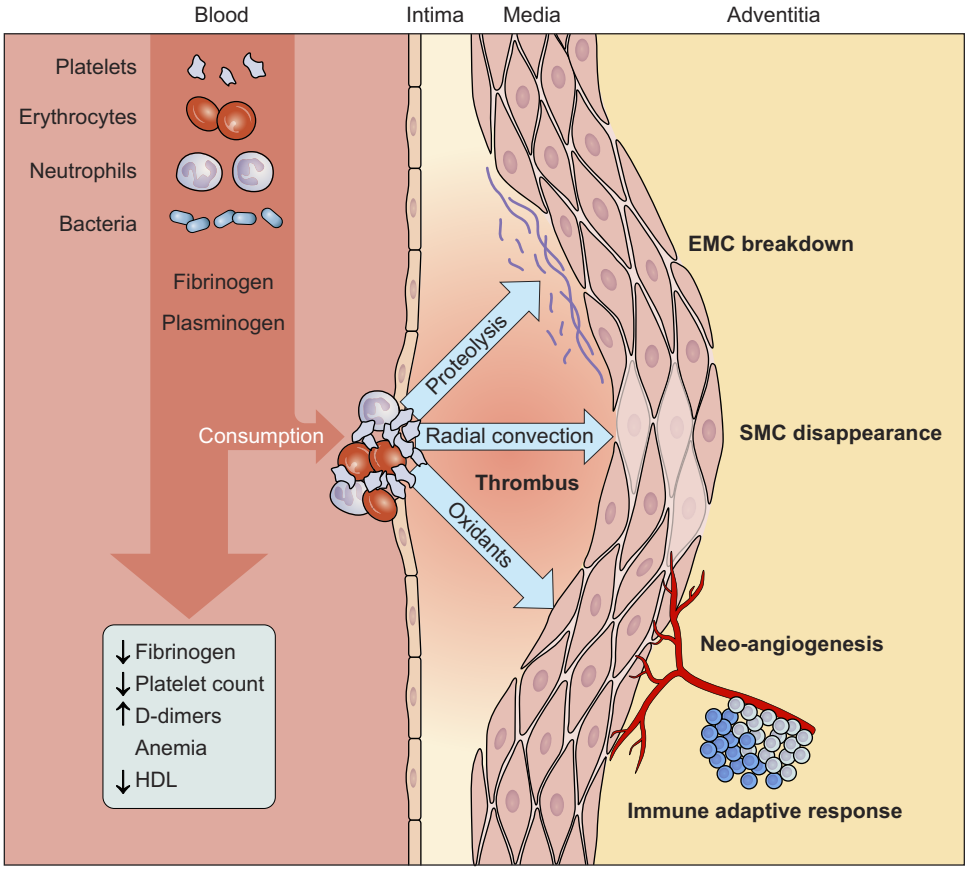

FIGURE 15. Consumptive activity of the intraluminal thrombus (ILT) in abdominal aorta. Since the ILT is not occlusive, the flowing blood continuously nurtures its luminal pole with blood plasma and particulate components. Therefore, the ILT is an active neo-tissue with a spatial and temporal organization, continually undergoing luminal renewal and abluminal fibrinolysis. Since the ILT is highly porous, all the solutes and microparticles generated within it are outwardly convected towards the wall, promoting its proteolytic and oxidative degradation, leading to smooth muscle cell (SMC) and extracellular matrix (ECM) disappearance. In some cases, this biological activity of the ILT can be so intense that it can have a systemic impact on the circulating blood composition: consumptive coagulopathy, consumptive anemia, and high-density lipoprotein (HDL) consumption due to apo A oxidation within the ILT.

tion (359). Whatever the etiology, including deficit in energetic support, the SMC-matrix connections at the contractile-elastin unit are variably altered in human TAA (240).

Certain rarer mutations are of particular physiopathological interest in TAA. Mutations in methionine adenosyltransferase 2 (MAT2A) are associated with a high risk of the hereditary form of TAA (195). Since MAT2A is an enzyme that transforms methionine into *S*-adenosylmethionine, the universal methyl group donor, its loss of function mutation directly impacts the epigenome, including DNA and histone methylations, and interferes with sirtuins (524) (see below), increasing the metabolic vulnerability of the ascending aorta. Likewise, GLUT10 (a glucose transporter) mutations are involved in arterial tortuosity (elongation) and aneurysms (82). Loss of function of GLUT10 directly impacts mitochondrial function and ROS production within SMCs (519). Similarly, loss-of-function mutations in FOXE3, a fork head transcription factor, are also associated with a hereditary risk of developing TAA (288). Foxe3, a member of the FoxO family, targets genes involved in DNA repair, glucose metabolism, and energy homeostasis by buffering ROS (546). Similarly, nicotinamide phosphoribosyltransferase (NAMPT) and NAD fueling participate in the maintenance of arterial wall integrity (569). NAMPT is expressed in human SMCs of healthy aortic media, but this expression is reduced in TAAs, whatever their etiology. This significant decrease is negatively correlated with the ascending aorta diameter, associated with an increase in strand breaks of unrepaired DNA and methylation of the NAMPT promoter in human TAA tissues. A complete deciphering of this pathway, including the role of poly(ADP-ribose) polymerase (PARP) was established through SMC-selective transgenic approaches in mice (569). Therefore, these mutations and signaling provide evidences of links between SMC energetic demands, chromatin integrity, and nuclear pulsatile mechanotransduction in the physiology of the aortic wall, negative modulation with time (aging), and defects in pathology.

In addition to the classical form of TAA, and among the genetic determinants of disorganization and dysfunction of the ECM, are the rare haplo-insufficiency (supravalvular aortic stenosis, sVAS) or dominant negative mutations (cutis laxa, ADCL) of the elastin gene. Larger deletions including the elastin gene and other neighboring genes (Williams-Beuren syndrome, WBS) are phenotypically different (131). In addition to predominant elastin fragmentation in the skin, ADCL can induce pediatric aneurysms and tortuosity of the conductance arteries (198). Elastin haplo-insufficiency (SVAS and WBS) preferentially induces localized (ascending aorta, pulmonary artery, coronary ostia) endovascular SMC proliferation and a systemic decrease in arterial diameter (258), a decrease in aortic compliance (148), an increase in stiffness, and frequent hypertension, potentially related to a low diameter-dependent increase in frictional

forces, due to diffuse SMC proliferation in conductance arteries (202). Localized SVAS can be detected after birth and can evolve throughout growth. SVAS is associated with an increase in arterial wall thickness, an increase in SMCs and elastic lamellae, with a decrease in elastin density and content. In SVAS, collagen remains unaltered and, as described above, is mainly involved in resistance to rupture. Thus vascular Ehlers-Danlos syndrome (vEDS), a rare disease due to pathogenic mutations in COL3A1, is characterized by repeated acute events of localized dissections, acute arterial rupture, postinfarct ventricular ruptures, pneumothorax, and varicose veins (80). In this context of high vascular wall fragility, surgical and endovascular procedures are always extremely difficult and risky.

TAA is one of the clinical and biological models in humans for studying the epigenetic impact and inheritance of SMC physiology (180), pathology, and clinical translation (54). Whatever the etiology, TAAs are characterized by an increase in arterial wall permeability that enhances convection of plasma zymogens through the wall. In particular, a defect in the SMC contractile response to tensile stress (88) and a degraded elastin network considerably increase the radial transport of plasma zymogens (539), including plasminogen (56), across the wall. In this context, conversion of plasminogen into plasmin by SMC activators (t-PA and u-PA) leads to degradation of the ECM, inducing SMC detachment and anoikis (338), therefore promoting arterial wall fragility. Nevertheless, the SMC is also able to synthesize antiproteases, particularly protease nexin-1 (PN-1), a tissue serine-protease inhibitor, which is able to block the fibrinolytic system (61). Of note, the primary function of mural cells in evolution (zebrafish) is to limit proteolytic injury to maintain arterial wall integrity [see above (507)]. Although SMCs are not able to clear active proteases but by secreting antiproteases, which form complexes with active proteases (but not with zymogens), SMCs acquire the ability to clear these protease/antiprotease complexes by endocytosis via the LRP-1 scavenger receptors (59).

Progressive dilation of the ascending aorta increases the tensile stress exerted on the wall, subjecting SMCs to an increase in pulsatile mechanical stretching, stimulating mechanotransduction, including at the nuclear level (see above). In one of our studies on TAA, we observed that there is a complete dissociation between the TGF-β pathway and SMAD2 expression in TAA (175). Nuclear translocation of *p*-SMAD2 is constitutive in SMCs of TAA, whereas TGF-β is highly localized. Moreover, this epigenetic modification is present in cultured SMCs from TAA, passed on through successive cell culture passages, and is SMC-specific (the epigenetic shift is not present in adventitial fibroblasts) (176). We deciphered the molecular mechanism of this constitutive SMAD2 expression and activation as an epigenetic phenomenon. It involves alternative splicing on the SMAD2 promoter and formation of an activator complex, independent of TGF-β, associated with a shift in Myc as a repressor, by P53 as an activator transcription factor, PCAF and GCN5 as HAT (466, 557) and TRRAP (transformation/transcription domain associated protein), leading to chromatin remodeling involving H3K9 acetylation (178). We then explored whether this epigenetic regulation also exists in human aortic tissue in acute dissections of similar etiologies. We observed that there is no epigenetic shift in SMAD2 expression and activation in aortic dissection, whereas protease activation is similar (plasmin, t-PA, u-PA). In contrast, in aneurysms, SMAD2 overexpression and activation lead to constitutive synthesis of antiproteases, such as PN-1 and PAI-1 (tissue serpins), by SMCs, independently of TGF-β (177). Therefore, SMCs of aneurysmal origin are more resistant to proteolysis than SMCs from acute dissections (177). In this context, we can conclude for the first time that protective chromatin remodeling takes place in chronic dilation in response to a progressive increase in tensile stress, whereas this protective mechanism does not operate in cases of acute arterial wall rupture (352).

As in atheroma, TAA can be associated with a moderate development of inward neoangiogenesis, but in contrast to atheroma, this intramedial neoangiogenesis is not dependent on VEGF but rather on angiopoietins (268).

The third localization of arterial aneurysms is intracranial. ICAs are associated with a risk of rupture and a high neuronal mortality and morbidity. ICAs are usually saccular aneurysms, developing on or near bifurcations. Localized specific hemodynamics are constantly involved in ICA development and rupture (162). Due to complete swirling flow in the aneurysmal sac, a cup-like ILT usually develops in ICA and remains biologically active, as in AAA (319). The relationship of ICA to local hemodynamics was also exemplified by the experimental model of Hashimoto, in which the association of a unilateral carotid ligature with systemic hypertension could lead to anterior aneurysm formation in rats (215–217). In this experimental model, hypertension and a high flow in the anterior communicating artery are necessary to obtain aneurysmal development. Hypertension alone or ligature alone is not sufficient for aneurysm formation. Sometimes, the addition of β-aminopropionitrile (BAPN), a lysyl-oxidase inhibitor that prevents the formation of covalent bridges in the ECM, is also necessary to obtain aneurysms. The Hashimoto model can be analyzed with regards to genetic TAA, induced by mutations of contractile proteins (see above). In TAA, these loss-of-function mutations on myosin, actin, or MLCK or gain-of-function mutations of PKG-1 lead to aneurysm formation because of the lack of adaptation of SMC contractile function and tensegrity (elastin-contractile unit) in response to tensile stress (359). Physiologically, a localized increase in tensile stress must be functionally compensated by a myogenic contraction response and structurally by

hypertrophy/hyperplasia of SMCs. In the Hashimoto model, localized increase in flow and shear stress activates NO release by the endothelium, causing subjacent relaxation of SMCs not adapted to hypertension and sensitizing the high-flow segment to dilation and the convection of zymogens through the wall. Likewise, a mutation in angiopoietin-like protein 6 (ANGPTL6) is also a genetic substrate for a hereditary form of ICA (60). ANGPTL6, also known as angiopoietin-related growth factor, is synthesized by the liver (not by SMCs) and circulates in the plasma, promoting angiogenesis (403) and playing a trophic role in other tissues (404). In the ANGPTL6 genetic form of ICA, the plasma level of ANGPTL6 in patients is one-half of that of controls (60). Lastly, the development of ICA is highly dependent on the integrity and geometry of the circle of Willis (118, 264). In this context, hypoplasia of one segment of the circle of Willis could create localized imbalance in blood flow (392), and any change in its geometry (angulation) could induce impingements on bifurcations (339, 549).

In clinical human ICA, the delayed gadolinium-enhanced imaging of the wall after MRI angiography has been proposed as a prognostic marker of gravity (469). This delayed enhancement could reflect different phenomenona including a luminal thrombus and an increase in wall permeability.

E. Heart Failure

Whatever its etiology (postinfarct, valve diseases, primitive cardiopathies, myocarditis, fibrosis) and its evolutive clinical stage (conserved or decreased ejection fraction), left-sided heart failure (HF) is characterized by an increase in end-diastolic pressure (EDP) within the LV cavity. Therefore, HF is hemodynamically a direct application of the energy transfer and dissipation in which the increase in residual EDP provides evidence of the transfer of mechanical energy of motion (Ek) into pressure (Ep) **(FIGURE 16)**. This is directly related to the functional geometry of the ventricular cardiac band (537), which aligns the LV cavity on the aortic orifice in isovolumic protosystolic contraction (337) and similarly promotes the most efficient filling flow during diastole (72, 538). These LV wall alignments promote the physiological kinetic energy yield of ejection. In contrast, this performance is limited by global or localized dyskinesis or akinesis of the LV wall in HF. In these cases, there is dissipation of velocity vectors during systole (356) and diastole (22) in relation to changes in functional topology of the LV wall motion (long-axis versus short-axis, ultrasound and RMI) (138, 422). This change defines an increased LV impedance to ejection and filling, whether the ejection fraction is conserved or not, increasing the mechanical work of the heart and thus causing a corresponding increase in metabolic demand. Moreover, this defect in pumping ability yield can be amplified by the electrical desynchrony sometimes associated with HF (423). This hemodynamic overload could evolve toward dilatory remodeling leading to decrease in ejection fraction (518).

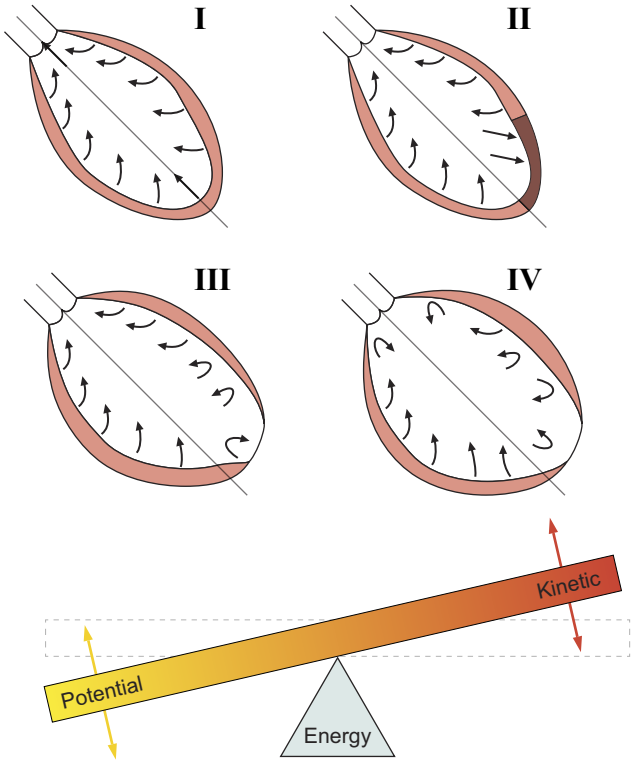

FIGURE 16. Heart failure. Evolution of heart function after left ventricular myocardial infarction from healthy function (I) to congestive heart failure (IV). The intermediary steps (III, akinesia, and IV, dyskinesia) represent compensated stages in which the ejection fraction may be conserved. All stages from II to IV are associated with an increase in end-diastolic left ventricular pressure (EDP) which defines heart failure, in both compensated and decompensated stages. This increase in EDP provides evidence of the change in the balance between kinetic and potential energy in the left ventricle (LV) and dissipation of velocity vectors within the akinetic or dyskinetic fibrous scar, and the transfer from Ek to Ep within the LV cavity.

The endocrine natriuretic function of the myocardium is also modified by the change in mechanotransduction associated with HF (347). Secretion and synthesis of the NPs, first atrial natriuretic peptide (ANP), identified physiologically by de Bold in the atrial granules, which are sensitive to salt and water retention (115), and then brain natriuretic peptide (BNP), discovered later (333). The ANP gene (*Nppa*) and the BNP gene (*Nppb*) are derived from the fish archaic CNP-3 gene through duplication and divergence (247). *Nppa* and *Nppb* are paralogous genes (317), abundantly expressed in both atrial and ventricular myocardium during embryonic and fetal life, but their expression is strongly reduced in the LV after birth (482). In the context of HF, regardless of the model, the fetal genomic program is reactivated. Indeed, we were the first to describe ventricular myocardial recruitment (hyperplasia) in response to hemodynamic diastolic overload in an experimental model, with a negative gradient from the base to the apex (295). The

mechanism of this ventricular recruitment for both ANP and BNP synthesis and secretion has been recently identified as chromatin remodeling in cardiomyocyte nuclei (229, 414), similar to what was described for the juxtaglomerular apparatus and renin secretion (see above). Expression of *Nppa* and *Nppb* is regulated via *cis*-regulated DNA elements. The *Nppa* and *Nppb* genes form a cluster separated by kilobase pairs of the DNA sequence forming a chromatin loop (topologically associating domains). This epigenetic control of expression potentially involves H3K27 acetylation mediated by p300 and HAT, a super enhancer locus, and RNA polymerase II (229). Nevertheless, although the transcription factor Nkx2–5 is involved in fetal regulation of *Nppa* and *Nppb* expression in the ventricle, the transcription factor involved in the response to diastolic mechanotransduction in the ventricle of compensated or decompensated HF remains to be identified (568). Therefore, the circulating level of NPs or their precursors (NTerminal-Pro BNP) remain the best biological markers of HF. Similarly, NP and cGMP concentrations in plasma and urine are the main pharmacological markers of neprilysin inhibition in HF (181). The consequences of this energy transfer from flow to pressure, including pulmonary consequences, are the main determinants of the clinical expression of HF (43).

Epicardial adipose tissue (EAT), the visceral fat surrounding the myocardium (320), particularly along the coronary arteries and on the anterior surface of the ventricles and apex, is an integral component of the cardiac functional anatomy (163) and is able to release fatty acids as metabolic substrates for cardiac muscle activity. Moreover, quantitative and qualitative changes in EAT are associated with atherothrombotic pathology of the coronary arteries, atrial dysfunction, and HF (409). The published data are sometimes ambiguous in HF, reporting a decrease in relative EAT and its negative correlation with the LV remodeling index (125) or an increase in EAT mass associated with sympathetic desensitization in congestive HF (415, 574). EAT may play a cardiac role through its thermogenesis function, as a significant decrease in the thermoregulating gene expression and function of EAT in HF was reported (426). It is now well established that natriuretic peptides are adipogenic (at low concentrations) and/or lipolytic (at high concentrations) (36), controlling energy metabolism via the cGMP signaling pathway within adipocytes (373). However, this effect depends on both the dose and the time (172). Nevertheless, adipocytes are not the only cellular targets of natriuretic peptides, which also interfere with the renal epithelial cells via G-kinase II (96, 206), circulating neutrophils (379), and more recently reported, the mesenchymal progenitors and fibroblasts of EAT (263). For instance, it was recently shown that ANP drives the transition of tissue mesenchymal progenitors to adipocytes in the atrial epicardium (509). Likewise, NP-clearance receptor knockout increases ANP bioavailability for NPR-A and protects against TGF-β-dependent atrial fibrosis in atrial fibrillation-susceptible mice (440), whereas Egom et al. (134) reported increased fibrosis and slowed atrial conduction in natriuretic peptide receptor type C (NPR-C) knockout mice. Therefore, in addition to the prognostic value of members of the NP system as biomarkers, the pharmacological manipulation of the NP system by agonists or potentiation by neprilysin inhibition or inhibitors of cGMP degradation remains to be explored clinically (556).

In addition to the pathophysiological aspect of HF, interventional therapeutics using left ventricular assist devices raise the question of the specific role of pulsatility. Usually these rotary pumps deliver a continuous flow rather than a pulsatile one (365). Despite impressive clinical results, the use of these devices induces mid-term complications including spontaneous bleeding, aortic valve disease, thromboembolic events, and impaired renal function. These pathological events are related to the absence of flow pulsatility and continuous endothelial high shear stress, impacting hemostasis, in particular the loss of function of HMW multimers of vWF function (233), hemolysis, reverse remodeling of the left ventricle, and aortic valve insufficiency (418). Therefore, these observations provide evidence that pulsatile flow and, potentially, pulsatile pressure are important determinants in the maintenance of cardiovascular (CV) structure and functions.

F. Hypertension and Aging

1. Observational studies in humans

The relationship of the arterial tissue aging process (mainly aorta and carotid) to hemodynamic load has been largely documented over the last 50 years through the detailed study of human aging cohorts with follow-up and noninvasive (ultrasound, applanation tonometry, etc.) methods for measuring intermediate hemodynamic parameters focused on the loss of arterial wall elasticity. These developments were associated with a similar approach in human arterial hypertension, particularly in senior hypertension compared with that of younger patients, diabetes, and chronic kidney diseases. These observational data were recently reported and synthesized in a remarkable book (395) (multinational 56 coauthors) devoted to the physiological aging of hemodynamics and arterial function in gerontology and promoting the new paradigm of "Early Vascular Aging" in hypertension. Several hemodynamic parameters were analyzed, including the measurement of pulse wave velocity (PWV) as a functional marker of arterial wall stiffness, intima media thickness (IMT) of carotid arteries, arterial diameters and distensibility concomitantly with arterial pulse pressure, reflection waves, and coupling between large-conductance arteries and distal resistance arteries and arterioles.

These hemodynamic measurements were used to follow-up several cohorts of normotensive and hypertensive people.

The final and global results attributed prognostic value for mortality and cardiovascular events (coronary artery disease, stroke, heart disease, etc.) to the age-dependent rigidity of the arterial tree, dependent or independent of other CV risk factors (cholesterol, smoking, metabolic syndrome, sex hormones).

This progressive time-dependent stiffness is related to remodeling, consisting of the adaptive (physiological) or maladaptive (pathological) changes in arterial structure-function relationships. Aging remodeling differs between large-conductance arteries and resistance arteries and arterioles but predominates in large arteries, whereas remodeling of arterioles predominates in hypertension. Few studies have been conducted on the effect of aging on small arteries in humans (380, 402) in comparison to changes in hypertension and the changes of large conductance arteries in aging. These changes in resistance arteries essentially have been investigated in experimental animal models of different ages (296). In healthy rats, aging is associated with SMC hypertrophy and an increase in the collagen-to-elastin ratio leading to increased stiffness. In aging sheep, small mesenteric arteries have an increased lumen diameter and adapted media thickness (Laplace law), leading to no change in the lumen-to-wall thickness ratio, defining outward hypertrophic remodeling with no important change in mean (Poiseuille law) or in pulse pressure (402). These data fit well with the observed absence of change in peripheral resistance with aging in humans (293). In humans, as well as in rats (350), conductance arteries (aorta, carotid, and femoral arteries) also enlarge with aging with the persistence of a sexual difference (female diameter $<$ male diameter) (446, 552) in relation to elastic fiber fragmentation due to their biomaterial fatigue (repeated stretching). The increase in large artery stiffness is due to an increase in collagen content associated with this elastic fiber fragmentation. At the SMC level, the tensile cytoskeletal components also become more rigid (613), leading to a new paradigm of "the SMC stiffness syndrome" (478).

In 1956, Denham Harman proposed a theory of the aging process that was dependent on oxidation, directly dependent on metabolic activities and time (213), and therefore, dependent on the mitochondrial respiratory chain and cell redox status **(FIGURE 17)**. In the last 10 years, it was demonstrated that the enhancement of mitochondrial oxidative activities and cytosolic oxidases (510) and the decline in their control by SOD (612) occur with aging, aortic enrichment in collagens, impoverishment and fragmentation of elastic fibers, increase in arterial stiffness, and decreases in the compliance and semiology of heart overload in animals (406). A similar increase in ROS production was reported to be involved in hypertension, focusing on the detrimental role of oxidases not only in the arterial wall (endothelium and media) but also in the kidney and CNS (312).

In the context of CV aging and pathologies in mammals, epigenetic sirtuin1 (Sirt1) signaling pathways (269) play a potential protective role in the prevention of CV disease (275). Sirtuins are members of the deacetylase/transacetylase enzymatic family targeting both histone and nonhistone acetylation. There are seven isoforms of sirtuins in humans, which have slightly different molecular targets with cooperative or opposing effects, rendering the deciphering of their physiology sometimes complex. Sirtuins are derived from an ancestral gene, silent information regulators (Sir2), which contributes to increased longevity in invertebrates, in mammalian experimental models and, potentially, in humans (47). Sirtuin enzymatic activities are dependent on nicotinamide adenine dinucleotide (NAD+) as a substrate (reviewed in Ref. 567). The beneficial effect of Sirt1 on vascular aging, senescence, hypertension, and atherosclerosis appears to be related to its capacity to activate endosome-lysosome functions, in particular in the context of autophagy in aging (462). At the vascular cell level, the majority of studies focus on endothelial cells and on the ability of Sirt1 to promote angiogenesis, activation of NO synthase, regulation of autophagy, apoptosis, oxidative pathways, and others (306). Studies focusing on Sirt1 in heterophagy are rarer. Nevertheless, comprehension of the role of Sirt1 in SMC physiology is currently extending. Sirt1 activation prevents the vasodilation impairment associated with aging by enhancing guanylate cyclase expression (197); promotes the specific expression of contractile proteins (510), including SM22α and downregulation of NF-κB (488); and protects against DNA damage (182). Sirt1 enhances SMC migration and proliferation (561) and prevents the osteoblastic phenotypic shift of SMCs and the ensuing vascular calcifications (29, 37). It also prevents foam cell formation (608) and therefore plays a potentially protective role in atherosclerosis development (607). One of the translational interests of the sirtuin system is that there are natural pharmacological activators (resveratrol, micromolar range of affinity) and inhibitors of Sirt1, and development of synthetic compounds with better affinities is currently underway (567). Another way to stimulate sirtuin is to improve the bioavailability of the substrate NAD+ via NA phosphoribosyl transferase activity (Nampt) (569). Members of the sirtuin family are located in the mitochondria, where they regulate energy and redox activities (525).

At this stage, it is possible to propose that mitochondrial and cytosolic oxidative stress provide the time-dependent link between the metabolic physiological necessity of arterial tone, SMC tensegrity and vasomotricity, and the pathological increase in this energetic demand with structural and functional changes of the arterial wall observed with aging and hypertension. In this paradigm, time-dependent repeats of biochemical oxidative stress and its consequences translate the biomechanical fatigue due to hemodynamic loads.

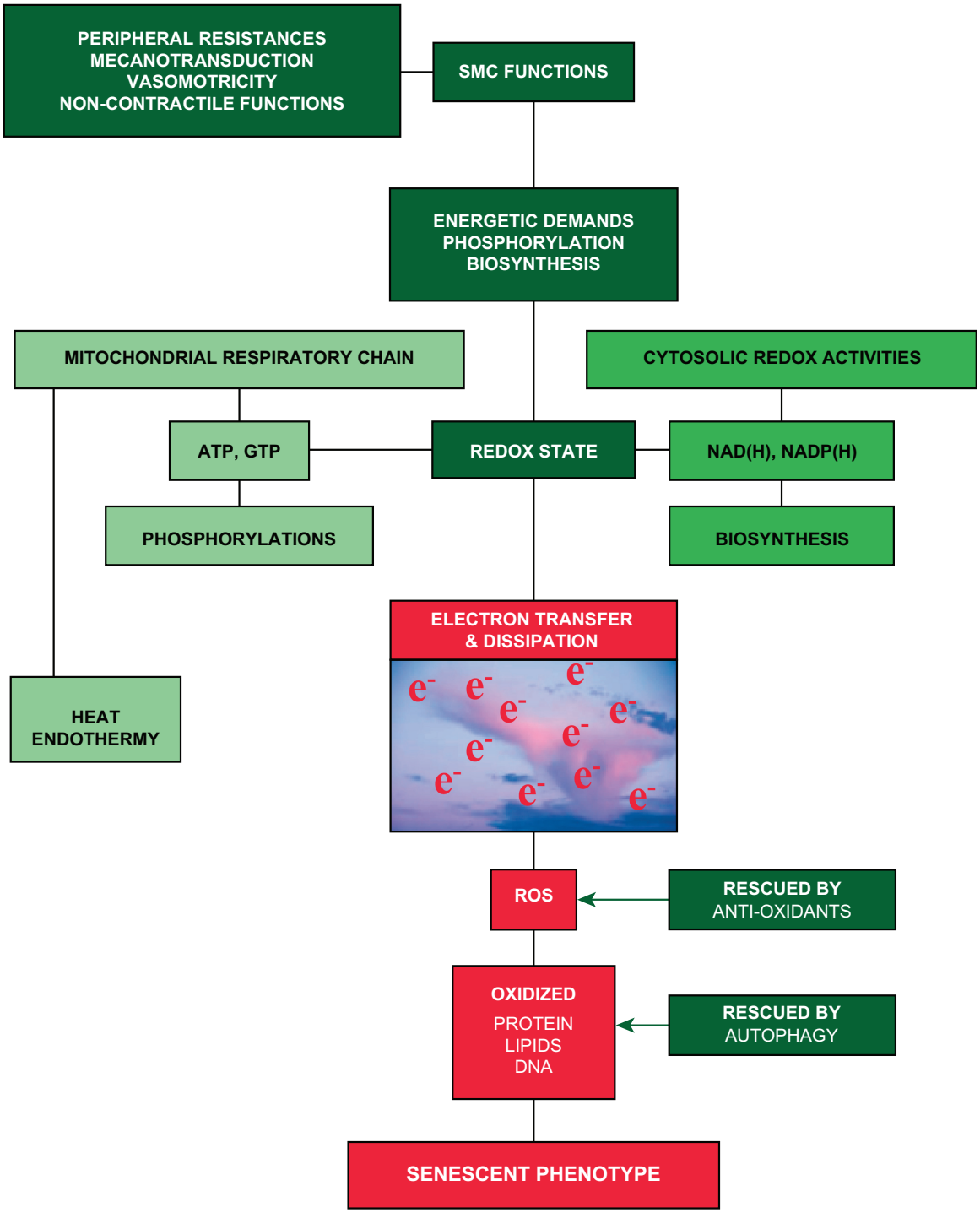

FIGURE 17. Schematic diagram showing how smooth muscle cell (SMC) metabolic activity generates oxidative stress. There are two predominant pathways that release free electrons and reactive oxygen species (ROS) in SMCs: the respiratory chain in mitochondria and NADH/NADPH oxidase in the cytosol. These two pathways are, respectively, directly involved in the generation of biochemical energetic substrates, ATP and GTP for phosphorylation, and NAD/NADP regeneration for biosynthesis and polymerization.

2. Progeroid diseases

In this context, the rare genetic disorders, progeroid syndrome, are interesting models of pathological accelerated aging processes.

Hutchinson-Gilford Progeria Syndrome (HGPS) is a very rare genetic laminopathy related to de novo mutation in the prelamin A gene (117, 139), which greatly impedes the final maturation of lamin by the zinc metalloproteinase ZMPSTE24, leading to accumulation of farnesylated

prelamin (progerin) in the rim of the nuclear envelope (208). HGPS is characterized by growth retardation, thin skin, hair loss, joint diseases, lipodystrophy, and most importantly, cardiovascular diseases. Invariably these patients die from myocardial infarction or stroke related to atherothrombotic events at around 20 yr, whereas their lipid profiles are normal, but their arterial wall is highly calcified, mimicking, at least in part, aging arteriopathies (405). Since HGPS is very rare, human pathological data are limited to case reports. In this context, the accumulation of progerin considerably changes the mechanical properties of the nuclear envelope, making it resistant to the biochemical extraction of lamin and limiting its elastic recoil and envelope deformability in response to stretching, resulting in lamin-forming paracrystals (111). Arterial histopathology concordantly demonstrates loss of SMCs in the media of conductance arteries, including the aorta and carotid and coronary arteries, associated with a high degree of calcification, some lipofuscin deposition, an increase in collagen content of the media and the adventitia and atherosclerotic plaque formation (4, 31, 405, 449, 500, 501). Therefore, to better understand HGPS and its impact on physiological cardiovascular aging, transgenic models have been created (547), including specific targeting of mutation expression in SMCs or myeloid cells (209). These transgenic approaches are always associated with loss of SMCs, as in human progeria pathology. Moreover, specific mutations targeting SMCs reproduce the arterial pathology, whereas targeting macrophages has no consequences. Crossing an SMC-targeted mouse with the apo $E^{-/-}$ hyperlipidemic mouse considerably accelerates the development of atherothrombotic plaques and complications, whereas crossing apo E−/− with macrophage-targeted progerin has no additive effect (209). In a similar way, intranuclear and cytosolic vesicles are observed in aortic SMCs of these transgenic mice, and SMC disappearance predominates at branch points, colocalized with more important fibrosis in the adventitia. These data were recently extended to endothelial flow-dependent cell mechanotransduction (408). An endothelium-specific progeria mouse model developed endothelial dysfunction (a decrease in NO generation), cardiac hypertrophy, and perivascular fibrosis. In contrast to the SMC model, endothelial progeria did not affect medial SMCs but suppressed the development of arterial calcifications, suggesting a direct role of SMC death in calcium precipitation on inorganic phosphates. At the nuclear level, progeroid SMCs showed misshapen nuclei and DNA damage promoting SMC death in response to stretch. Finally, but most importantly, disrupting the LINC complex between cytosolic actin and lamin partially rescues the arterial lesions (272). In contrast, since fishes have low vascular pressure and rare mural cells, inducing progeria in zebrafish results in the development of syndromic lesions without vascular injury or life shortening (282). These data provide evidence that the progerin rim in the nuclear envelope considerably modifies nuclear mechanotransduction in the arterial wall and potentially prevents the associated epigenetic adaptation of the SMCs, leading to catastrophic arterial disease.

Werner syndrome (WS) is also a genetically determined adult progeroid, multisystem disease, usually diagnosed later than HGPS, with a life expectancy of ~50 yr. The main causes of death are cancer, myocardial infarction, and ischemic stroke (407). Werner gene (WRN) encodes for the nuclear WRN protein, a helicase and exonuclease enzyme directly involved in DNA stability, repair, cell cycle, and telomere maintenance (297). WRN mutations in WS are loss of function, inducing DNA instability, progenitor exhaustion, and impairment of autophagy as well as increasing the oxidative stress within the target cells (297). HGPS and WS share the ability to induce high levels of vascular and valvular calcifications providing evidence of the ability of free normal or abnormal DNA (tissue phosphate exposure) to precipitate calcium in soft tissue, as also observed in association with physiological aging (108). These observations lead to a more comprehensive understanding of the interactions between chromatin dysfunctions as well as pathological and physiological aging (251). This susceptibility to aging could be related, at least in part, to the specific importance of mechanotransduction, particularly nuclear transduction, in the cardiovascular system. This paradigm is also confirmed by a population genetics study showing that common variants in WRN can impact the cardiovascular susceptibility to aging (102). It also opens up new opportunities to prevent interactions between aging and cardiovascular diseases, through NAD implementation and maintenance of sirtuin activity (142).

VII. SYNTHESIS AND CONCLUSION

The evolution of animal species involves numerous stages from invertebrates to aquatic vertebrates, transition forms to terrestrial life and finally mammals. These transitions were associated with numerous revolutions: exoskeleton to endoskeleton, gills to lung, fins to legs, cold- to warm-blooded, oviparity to viviparity, etc. This general evolution was accompanied by specific circulatory developments initiated by archaic heart motions, followed by changes in the circulatory system from an open system to a closed in-series system, in which the bloodstream developed with limited resistance to flow. This was followed by in-parallel circulatory systems in mammals (and birds), including a highly pressurized arterial compartment, as initially observed and described by William Harvey and a capillary compartment as described by Marcello Malpighi, necessitating an important mechanical energy dissipation between both. However, within Mammalia, dynamic evolution continued to occur with the progressive acquisition of upright posture (*Homo erectus*) associated with functional and structural brain development (*Homo sapiens*), which necessitated specification of the cerebral arterial circulation.

Fetal development of the circulation in mammals, particularly in humans, recapitulates the footprints of phylogeny and escapes: blood mixing and shunting, low pressure, predominant role of flow, exothermy, etc. **(FIGURE 18)**, but exaptation (escape) of arterial pressure takes place during ontogeny essentially regulated by pulsatile flow and relative hypoxia. Peripheral resistance (frictional forces) appears at birth and continues to increase during growth, generating high levels of hemodynamic constraints which force the specific differentiation of the arterial tissues and the plasticity of SMCs. This adaptive development deals mainly with epigenetic control of gene expression, involving, at least in part, mechanotransduction related to the balance between Ek and Ep.

The guiding principle of this complexification of cardiovascular biology is the structural and functional adaptation of the circulatory system to the specific metabolic demands of each individual organ's activity, integrated in general evolution. In this paradigm, circulation ensures the basal vital metabolic support to organs but also regulates the dynamic adaptation (variable part) of this support to the organ's specific functional activity. This functional adaptation necessitates the acquisition of peripheral resistance to flow via a progressive increase in frictional forces in the arterial part of the circulation (arterial tone) and the ability of local activity to inhibit this tone (local active vasodilation). Therefore, high arterial pressure is a direct consequence of this teleonomy, defined by peripheral resistance to flow and impacting left ventricular work (afterload). The phenotypic evolution of the circulation, and particularly its arterial part, fits well with the idea of "correlated progression" developed by T. S. Kemp (267a) as an integrated model for evolution, in which phenotypic traits are mutually interconnected. In circulatory evolution, the phenotypic arterial traits are vasomotor tone and the ability to vasodilate, arterial pressure, layered structure of the arterial wall, multiple arterial bifurcations, left ventricular functional anatomy, etc. and the intervening connections are the convection of solutes through the wall, hemorheology, mechanotransduction, plasticity of vascular SMCs, etc. Nevertheless, the own constant activity of the circulatory system particularly LV and arteries are energy consumptive, including the active structural and functional maintenance of the arterial wall throughout the life duration.

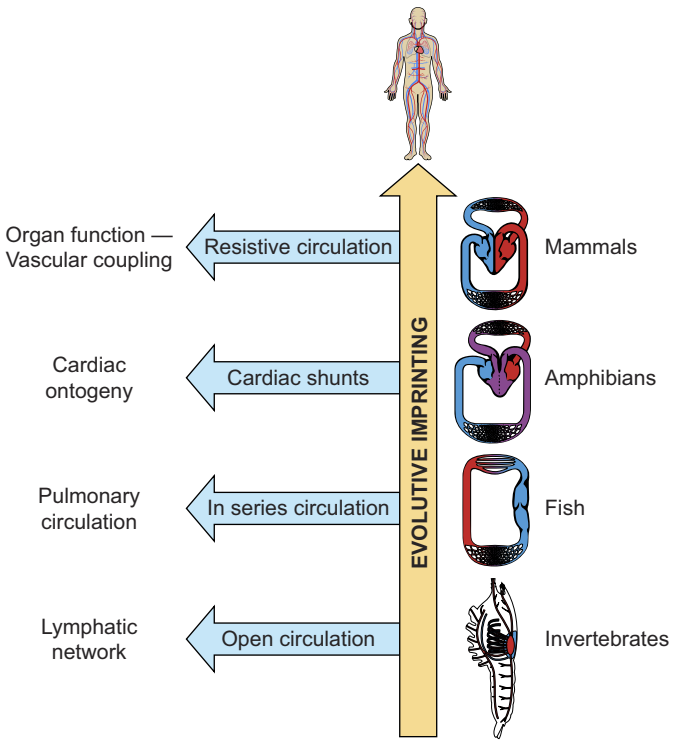

FIGURE 18. Footprints of evolution memory on the human circulation.

This correlated progression completely integrates the general evolutive scheme of gain of activity, minimal work, and efficiency. These phenotypic traits and connections are mainly under epigenetic control. However, this "correlated progression" is also the most common cause of cardiovascular frailty in humans, including the high prevalence of arterial/LV diseases.

VIII. FUTURE DIRECTIONS

In this concept many important physiological pathways remain to be further explored:

- The mechanism by which the different stages of circulatory system evolution footprint the ontogeny of the circulation in mammals and particularly in humans. Potentially epigenetic memories predominate in these pathways, but regulations of gene expression are probably multiple and diverse, involving DNA methylation, histone acetylation and methylation, miRNA, etc. It is potentially a big challenge to identify specific patterns of dynamic pathways controlling the different stages of fetal development in mammals.
- To develop new technologies able to analyze the chromatin topology such as Chromosome Conformation Capture (3–4C) extended to high-throughput 3C (Hi-C), deciphering the three-dimensional conformation of chromatin (13), applied to circulation development and SMC plasticity, in response to different chronic stimuli.
- The outward advective transport of soluble and microparticular plasma components through the wall is now well established, but rarely taken into account in physiology and pathology. Moreover, the fact that these plasma components interact or not with matrix and/or cellular elements of the wall is one of the driving forces for atheroma development, but all arterial pathologies are impacted by outward mass transport, and the role of convection has not yet been explored in many of them.
- Similarly it is of importance to further analyze the impact of RBC collision with the wall and to define the

role of this collision in the genesis of oxidation in relation to the catalyzer role of hem and Fe^{2+}.

- To measure the clearance capacity of the SMCs, i.e., their ability to endocytose soluble components and to phagocytose particulate ones, and to metabolize them.
- Therefore, to differentiate autophagy from heterophagy in the context of pathology and of physiological aging.
- To identify more precisely the impact of SMC contraction/relaxation on the function of conductance arteries: effect on compaction, permeability, delamination, rigidity, proximal reflection wave forms, etc.
- Biophysical properties of blood and arterial wall are potentially the main cause of CV disease. Biophysical causation is now under acceptance for understanding fundamental cell biology (48). We need to continue to work on the role of gravity and of hemodynamic as driving forces of CV pathologies.
- In particular, it will be important to develop tools (ultrasound, MRI) in humans to be able to further analyze the role of mechanical energy transfer and/or dissipation in the vascular system and within the heart: local dissipation of velocity vectors, local impingement of flow on the arterial wall, local pressure reflection wave.
- And more precisely wall enhancement of delayed gadolinium retention in MRI angiography, potentially reflecting the convection principle.

Life is the organization of matter such that this organization adapts to partially escape from the universal laws, which largely govern the state of matter. This partial escape is transitory (time limited) and necessitates energetic support arising from a transfer of biochemical energy to organ functions, such as biomechanical kinetic and potential energy balance in the circulatory system.

GLOSSARY

Advection	The transport of substances by an associated kinetic fluid force: liquid flow, air flow, bulk motion, which can escape, at least partly, from gravity (horizontal motion).
CpG islands	DNA loci where a cytosine is followed by a guanine in the linear sequence of bases ($5' > 3'$ direction) with an intermediate phosphate.
Energy dissipation	A physical process by which energy becomes not only unavailable but irrevocable in any form (Merriam-Webster).
Exaptation	A shift in the function of a trait during evolution, a character whose origin cannot be ascribed to the direct action of natural selection (cooptation) (185).
First thermodynamic law	The law of energy conservation. The total energy (E) of a closed system is constant. Mechanical energy can be transformed from one form to another (energy transfer), producing work (Wikipedia).
Mechanical impedance	A measure of how much a structure resists motion when subjected to a harmonic force. It relates forces with velocities acting on a mechanical system. The mechanical impedance of a point on a structure is the ratio of the force applied at a point to the resulting velocity at that point (Wikipedia).
Paralogous genes	Homologous genes that have diverged within one species. Unlike orthologous genes, a paralogous gene is a new gene that holds a new function. These genes arise during gene duplication where one copy of the gene receives a mutation that gives rise to a new gene with a new function, though the function is often related to the role of the ancestral gene (Sciencing).
Percolation	(From latin *percōlāre*, "to filter" or "trickle through") refers to the movement and filtering of fluids through porous materials (Wikipedia).
Carl von Rokitansky (1804–1878)	A famous Austrian pathologist, one of the founders of the modern pathology discipline. Rokitansky performed and analyzed ~100,000 autopsies during his professional life. The full archives of his book, *A manual of pathological anatomy*, are accessible at the website https://catalog.hathitrust.org/Record/001575734/Cite; volume 4, page 262: "*It (atheroma) consists of an excessive formation and deposition of the lining membrane of the artery derived from the mass of blood, and at the same time*

	constitutes hypertrophy of this membrane."
Second thermodynamic law	The total entropy of a closed system remains constant, leading to a steady state. In spontaneous processes, the entropy increases, and the process is irreversible (Wikipedia).
Super enhancers	Loci of the genome that collectively bind a pattern of transcription factors in open chromatin, driving gene transcription involved in cell identity and inducing a new balance with constitutive gene expression and a potential shift in cell phenotype controlled at an epigenetic level (histone acetylation) (Wikipedia).
Teleonomy	The quality of apparent purposefulness and goal-directedness of structures and functions in living organisms brought about by the exercise, augmentation, and improvement of reasoning. The term derives from two words, *τέλος telos* ("end purpose") and *νόμος nomos* ("law") and means "end-directed" (literally "purpose-law"). Teleonomy is thought to derive from history and adaptation for success (Wikipedia).
Tensegrity	Also known as tensional integrity is a structural principle based on the use of isolated components in compression inside a net of tensional constraints which delineate the system spatiality (Wikipedia).

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