Pathophysiological studies have extensively investigated the structural factor in hypertension, including large and small artery remodeling and functional changes. Here, we review the recent literature on the alterations in small and large arteries in hypertension. We discuss the possible mechanisms underlying these abnormalities and explain how they accompany and often precede hypertension. Finally, we propose an integrated pathophysiological approach to better understand how the cross-talk between large and small artery changes interacts in pressure wave transmission, exaggerates cardiac, brain and kidney damage, and lead to cardiovascular and renal complications. We focus on patients with essential hypertension because this is the most prevalent form of hypertension, and describe other forms of hypertension only for contrasting their characteristics with those of uncomplicated essential hypertension. (Circ Res. 2015;116:1007-1021. DOI: 10.1161/CIRCRESAHA.116.303596.)

Key Words: arterial stiffness ■ arterioles ■ brain ■ heart ■ hypertension ■ kidney
Small Artery Alterations

Small Artery Remodeling

Resistance arteries play a crucial role in the control of blood pressure (BP). The main drop in hydrostatic pressure occurs at their site. Peripheral resistance in small arteries (lumen diameter <350 μm) and arterioles (lumen diameter <100 μm) accounts for 45% to 50% of total peripheral resistance,1–3 whereas capillaries (≈7 μm lumen diameter) account for 23% to 30%. The Poiseuille’s law states that resistance is inversely proportional to the radius to the fourth power. Thus, slight alterations in arterial lumen, either functional or structural, result in significant changes in arterial resistance.

Small Artery Remodeling in Essential Hypertension

Vasoconstriction, eutrophic remodeling with increased media-to-lumen ratio, changes in distensibility, decreased vasodilation reserve, and rarefaction characterize small resistance arteries in patients with essential hypertension.1–4,7–9 Mechanisms leading to alterations in vasomotor tone and endothelial dysfunction in hypertension will not be addressed in this review. Changes in distensibility and reduced vasodilatation reserved are described in a paragraph dedicated to the functional consequence of the remodeling.

The major part of the structural changes observed in patients with essential hypertension is a consequence of inward eutrophic remodeling.4,7–9 Inward eutrophic remodeling corresponds to a greater media thickness, a reduced lumen and external diameter with increased media-to-lumen ratio, without any significant change of the total amount of wall tissue, as indicated by an unchanged media cross-sectional area (MCSA). There is a rearrangement of the same amount of wall material around a smaller vessel lumen without net cell growth (inspired by figure in Ref. 14).

remodeling with a more evident contribution of cell growth including vascular smooth muscle cells (VSMCs) hypertrophy (volume increase) or hyperplasia (cell number increase).10 As hypertension progresses, it is possible but unproven that eutrophic remodeling may evolve toward hypertrophic remodeling under the combined influence of angiotensin II and endothelin-1, other growth factors, and high BP11 (Figure 1). Eutrophic remodeling has been also observed in spontaneously hypertensive rats (SHRs) and stroke-prone SHR.1 In patients with essential hypertension, eutrophic remodeling may represent a protective mechanism against the elevation of BP, ultimately preventing the rise in circumferential wall stress at the level of arterioles and capillaries which are unable to withstand it.

In humans, the determination of media-to-lumen ratio requires the analysis of a gluteal biopsy. Subcutaneous small resistance arteries are then dissected and mounted on a wire myograph, and media-to-lumen ratio is measured. A noninvasive alternative to the gluteal biopsy has been recently brought by the measurement of wall-to-lumen ratio of retinal arterioles using scanning laser Doppler flowmetry, a parameter that is significantly increased in never-treated patients with hypertension,12 and significantly correlated with the media-to-lumen ratio of subcutaneous small arteries.4

Rarefaction corresponds to the reduction in the number of interconnected small arteries and capillaries.16,17 Evidence of capillary rarefaction in human essential hypertension has been obtained by in vivo capillaroscopy of the nailfold microvasculature.16,17 Functional rarefaction (increased number of nonperfused microvessels) can progress toward structural rarefaction (anatomic absence of microvessels). Structural rarefaction may result from a destructive process or be the consequence of insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.18 For instance, the loss of shear stress in insufficient angiogenesis, in response to decreased bioavailability of nitric oxide.

Cellular and Molecular Determinants of Small Artery Remodeling

Growth, apoptosis, mild inflammation, fibrosis, and chronic vasoconstriction have been suggested to contribute to small
Angiotensin II is a major determinant of small artery remodeling because it increases VSMC growth, collagen deposition, and contractility and induces inflammation. The signaling events, which occur in response to the binding of angiotensin II to the angiotensin type 1 receptor in VSMCs, have been extensively investigated in animals and humans. Particularly, angiotensin II activates receptor tyrosine kinases, such as epidermal growth factor receptor, platelet-derived growth factor receptor, and insulin-like growth factor-1 receptor, and non-receptor tyrosine kinases, such as c-SRC. The angiotensin II:angiotensin type 1 receptor binding induces activation of NAD(P)H oxidase resulting in intracellular generation of reactive oxygen species, which influence redox-sensitive signaling molecules, such as mitogen-activated protein kinases, transcription factors, and matrix metalloproteinases.

In patients with essential hypertension and in high-risk hypertensive type 2 diabetic patients, the selective antagonism of angiotensin type 1 receptor, added to previous antihypertensive agents, improved remodeling of resistance arteries beyond BP control, compared with the β-blocker atenolol. In type 2 diabetic hypertensive patients, long-term treatment with the selective angiotensin type 1 receptor antagonist valsartan induced an upregulation of angiotensin type 2 receptors in VSMCs of resistance arteries, associated with an angiotensin type 2 receptor-mediated vasodilation in response to angiotensin II.

Studies in human VSMCs and of vessels from experimental animals have also demonstrated that aldosterone and endothelin exert remodeling effects by stimulating xanthine oxidase and mitochondrial reactive oxygen species generation. In patients with essential hypertension, the selective mineralocorticoid receptor blocker eplerenone, administered for 1 year, reduced resistance artery stiffness, decreased collagen/elastin ratio, and reduced circulating inflammatory mediators, by contrast to atenolol.

Apoptosis, which is increased in hypertensive resistance arteries, may be either a growth-related compensatory mechanism or a primary process. Apoptosis may compensate growth to maintain inward eutrophic remodeling. Apoptosis modulators, such as reactive oxygen species, nitric oxide, angiotensin type 2 receptor, and endothelins, which are all altered in essential hypertension, likely play a role. Low-grade inflammation, partly angiotensin- and endothelin-dependent, and triggered by increased oxidative stress, may induce growth factor-mediated extracellular matrix (ECM) remodeling. Immune and inflammatory cells, macrophages, lymphocytes, and the cytokines they produce, are present in the vasculature and play a role in the modulation of remodeling. Effector T-cells such as T-helper 1 (interferon-γ-producing) and T-helper 2 lymphocytes, as well as T-helper 17 and T suppressor lymphocytes, are involved in the remodeling of small arteries that occur under the action of angiotensin II.

The role of ECM in remodeling and stiffening is fundamental. Collagen are quantitatively (most abundant protein) and qualitatively (the stiffer) the first candidates explaining the alterations in structure-function in hypertension. Collagen is increased in mesenteric small arteries of SHR and subcutaneous resistance arteries in patients with essential hypertension. Fibronectin may also accumulate in the media of resistance arteries in stroke-prone SHR. Angiotensin II–stimulated fibrosis may involve transforming growth factor β and platelet-derived growth factor, as well as other growth factors, such as insulin-like growth factor and basic fibroblast growth factor. Intengan and Schiffrin have proposed that remodeling of the small arteries occurring in both humans and experimental models of hypertension implies a remodeling of the ECM. The remodeling of extracellular-vascular SMC attachment sites and the restructuring of vascular SMCs may in part be triggered by the adhesion molecules that mediate the anchoring to ECM components.

Functional Consequences and Target Organ Damage

The functional and structural changes of small resistance arteries are interdependent and influence the global hemodynamic and vice versa. Figure 2 depicts these bidirectional relationships. The proximal resistance arteries are the main site for vasoconstriction in hypertension. They are also the main site for structural elevation of resistance, through reduced lumen diameter accompanying eutrophic remodeling, and rarefaction. A chronic vasoconstriction has been suggested to be the stimulus for eutrophic remodeling, smaller lumen diameter, and reduced distensibility. The most distal resistance artery sites, which are crucially important for local flow distribution, are partly protected from pressure elevation by a raised resistance upstream.

Figure 2. Schematic representation of the relationships between eutrophic remodeling of small resistance arteries (white boxes) and associated functional consequences (gray boxes) in essential hypertension. TOD indicates target organ damage.
Small artery damage in essential hypertension leads also to impaired vasodilatation. This is essentially through impairment of the vasodilator reserve, i.e., the ability to increase blood flow with maximal vasodilatation. Folkow first showed that minimal forearm resistance to blood flow at maximal vasodilatation (ischemia, exercise, and local heating) was increased in primary hypertension (animal models and humans). This was confirmed by a large number of experiments. The increase in minimal forearm resistance is strongly in favor of a structural elevation of resistance in primary hypertension because vasomotor tone is abolished under these experimental conditions. Among the several vascular beds that may be concerned, the coronary circulation is particularly at risk. A significant correlation has been found between media-to-lumen ratio of subcutaneous vessels and either flow reserve in the forearm or coronary flow reserve, suggesting that small artery abnormalities can be simultaneously present in different arterial territories.

The structural changes of small resistance arteries are related to myogenic tone in a bidirectional manner (Figure 2). An increase in myogenic tone reduces lumen diameter at higher pressures. This phenomenon is a key determinant of blood flow autoregulation and stabilization of capillary pressure. The myogenic response to increased circumferential wall stress is inversely related to the diameter of the vessel, and resistance precapillary arteries show the largest myogenic constriction response. The arteriolar circumferential wall stress is thus maintained at normal or even lower values. Because an increase in wall stress is a stimulus for growth, then a normal myogenic tone can prevent growth despite high BP. Thus, in essential hypertension, both myogenic tone and eutrophic remodeling maintain a normal wall stress, thus prevent growth that in turn maintains eutrophic remodeling (Figure 2). Conversely, impaired myogenic tone, such as observed in vessels from hypertensive patients with type 2 diabetes mellitus or patients with secondary forms of hypertension, would not limit the rise in wall stress which accompany the elevation of BP, and hypertrophy would develop. The above evidence supports the theory that the myogenic properties of the vessels determine the processes that mediate structural changes in hypertension. However, the altered myogenic tone may be less important than the vasoconstriction related to chronic neurohumoral stimuli, for inducing hypertension.

In essential hypertension, the role of myogenic tone in the autoregulation of blood flow depends on the regional circulation. For instance, in the renal circulation, myogenic tone primarily mediates the autoregulatory response, a mechanisms which is responsible for protection from hypertensive injury. If renal autoregulatory ability is impaired, even modest increases in systemic BP are expected to be transmitted to the glomerular capillaries. The increased transmission of pressure manifests as a reduced BP threshold for glomerular injury and a linear relationship between BP and glomerulosclerosis. Because BP fluctuates continuously at multiple frequencies, hypertensive injury to the glomerulus can be considered as a consequence of an excess energy delivered to the target organ vasculature from continuously oscillating pressures. Observations obtained by Loutzenhiser et al using the in vitro perfused hydronephrotic rat kidney preparation have showed that when exposed to pressure oscillation presented at the heart rate (6 Hz), the afferent arteriole does not behave passively, but rather responds with a sustained vasoconstriction. Moreover, when the peak and nadir pressures are varied independently, only the peak signal corresponding to the systolic pressure determined the response tone. Thus, the afferent arteriole constricts when the systolic pressure is increased even if mean pressure is unaltered. Altogether, these results suggest that impaired myogenic tone of the renal circulation, such as observed in vessels from hypertensive patients with type 2 diabetes mellitus, reduces the autoregulation capacity and increases the baro-trauma because of high systolic BP, leading to glomerular injury. The specific features of the coronary and cerebral circulations, and their response to excessive pressure pulsatility, are described below.

Whether the eutrophic inward remodeling exaggerates the vasoconstrictor response to any stimulus, this potentiating the increase in total peripheral resistance and the rise in BP, remains debated even today. The pressor effect of vasoconstrictors could be amplified and interact with other factors to contribute to the maintenance of elevated BP even if the intrinsic response of vascular smooth muscle to these agents is not exaggerated. In patients with hypertension, the media-to-lumen ratio of subcutaneous resistance arteries is related to the morning rise in BP, suggesting that structural changes amplify the neurohumoral arousal reaction.

Increased myogenic tone and arteriolar vasoconstriction contribute to the protection of downstream capillaries but also promote functional rarefaction, ultimately leading to structural rarefaction. Capillary rarefaction, associated with small artery remodeling, impairs tissue perfusion and organ function via 3 main mechanisms: the tissue nutritive role in response to variations in demand, the capillaries protection against the potential damaging effect of BP increase, and the resistance to flow perfusion. For instance, intramyocardial coronary rarefaction impairs tissue perfusion and increases susceptibility in ischemia during high metabolic and oxygen demand.

Reduced distensibility of small resistance arteries has been variably observed in hypertensive humans and animals. Reduced distensibility can theoretically occur as a consequence of wall thickening if the elastic properties of the wall material remain unchanged despite remodeling (Figure 2). It is difficult to propose a unified image from the results of numerous studies because they are strongly influenced both by the origin of the small artery (distal or medium-sized arterial bed in animal models, or subcutaneous biopsy in humans) and by methodological issues, such as fixation, examination at low or high pressure, and determination of the stress–strain relationship over a certain range of BP. Reduced distensibility seems to develop with aging in hypertensive humans and animals. An increased distensibility of middle cerebral arteries has been observed in young SHR (5 weeks) compared with Wistar-Kyoto rats controls, whereas a reduced distensibility was observed at the same site when hypertension was well established (20–24 weeks); interestingly, a eutrophic remodelling was observed in both young and old SHR. Similar findings were observed in posterior cerebral arteries.
of stroke-prone SHR. Small arteries of young patients with hypertension have reduced stiffness, whereas an increased stiffness develops later.

The consequences of reduced distensibility on regional blood flow are not unambiguous. A reduced distensibility can contribute to narrow the lumen of small arteries at high BP levels, exaggerating the structural part of total peripheral resistance, thus reducing blood flow to target organs. However, according to Folkow, small artery geometric design and distensibility tend to be altered to an ideal extent, so that with ordinary changes in smooth muscle activity a normal flow range is maintained, despite elevations in both perfusion and transmural pressures and in resistance.

Because blood circulation goes from the heart to large vessels, and then to the small arteries, the latter are directly concerned by modification in hemodynamic conditions caused by alterations in large arteries. In the next section, we will describe the changes in large artery properties in hypertension.

**Large Artery Alterations**

**Large Artery Remodeling**

In essential hypertension, large artery remodeling is characterized by an increase in intima–media thickness (IMT) (about +15–40%), a lumen enlargement of proximal elastic arteries, and no change in the lumen diameter of distal muscular arteries. Wall thickening allows compensation for the rise in BP and tends to normalize circumferential wall stress, according to the Lamé equation

$$\sigma = \frac{P \times R}{h},$$

where stress is proportional to radius (R), pressure (P), and inversely proportional to thickness (h). We explain below the relationship between arterial wall hypertrophy and stiffness, and why circumferential wall stress of large elastic arteries is not normalized in essential hypertension despite hypertrophy.

The enlargement of proximal elastic large arteries with aging and elevated mean blood pressure has been extensively described in humans in studies using ultrasound, particularly high-resolution echotracking systems. Wall thickening allows compensation for the rise in BP and tends to normalize circumferential wall stress, according to the Lamé equation

$$\sigma = \frac{P \times R}{h},$$

where stress is proportional to radius (R), pressure (P), and inversely proportional to thickness (h). We explain below the relationship between arterial wall hypertrophy and stiffness, and why circumferential wall stress of large elastic arteries is not normalized in essential hypertension despite hypertrophy.

The enlargement of proximal elastic large arteries with aging and elevated mean blood pressure has been extensively described in humans in studies using ultrasound, particularly high-resolution echotracking systems. Wall thickening allows compensation for the rise in BP and tends to normalize circumferential wall stress, according to the Lamé equation

$$\sigma = \frac{P \times R}{h},$$

where stress is proportional to radius (R), pressure (P), and inversely proportional to thickness (h). We explain below the relationship between arterial wall hypertrophy and stiffness, and why circumferential wall stress of large elastic arteries is not normalized in essential hypertension despite hypertrophy.

If local pressure pulsatility plays a major role on aortic root enlargement, conversely the consequences of aortic remodeling on central BP remain unclear. By contrast to studies in hypertensives, studies in normotensives reported a negative relationship between central BP and aortic root diameter, ie, the smaller the lumen diameter, the higher the central PP. Lam et al suggested that the lack of aortic root dilatation, increasing characteristic impedance (Zc) and wave reflection, would be the cause of high central PP and systolic blood pressure (SBP). Altogether, these data suggest that excessive pulsatility favors aortic enlargement when the arterial wall is already damaged, for instance by the hypertensive disease or by an underlying genetic defect, like Marfan disease. By contrast, when the aortic wall is healthy, a reduced volume of the aorta can increase characteristic impedance (Zc) and generate wave reflection, and thus elevate central PP and SBP.

In hypertensives, wall thickening, BP increase and lumen enlargement, all conjugate to affect circumferential wall stress. At the site of hypertensive proximal elastic arteries, such as the CCA, the intima–media thickening is insufficient to compensate for both the enlargement of internal diameter and the rise in BP: circumferential wall stress is significantly increased compared with normotensives. By contrast, at the site of hypertensive distal muscular arteries, such as the radial artery, the intima–media thickening compensates for the rise in BP (lumen diameter is not enlarged), and circumferential
wall stress is not significantly increased compared with normotensives. The mechanisms explaining the maladaptive wall thickening of large proximal arteries in hypertension are not clear. Their understanding may benefit from studies in patients with chronic kidney disease, which showed an exaggerated remodeling pattern, ie, a thinner carotid wall despite a larger lumen diameter for a given BP, leading to a higher circumferential wall stress than in hypertensives. In hypertensive patients with chronic kidney disease, carotid wall stress has predictive value for decline in kidney function. The defect of arterial wall thickening could be caused by different mechanisms, involving an excessive ECM turnover, a lack of VSMC proliferation, or apoptosis.

Large Artery Stiffness

The wording arterial stiffness is a general term that refers to the loss of arterial compliance and changes in vessel wall properties. Compliance of large arteries, including the thoracic aorta that has the major role, represents their ability to dampen the pulsatility of ventricular ejection and to transform a pulsatile pressure (and flow) at the site of the ascending aorta into a continuous pressure (and flow) downstream at the site of arterioles, to lower the energy expenditure of organ perfusion. During ventricular contraction, part of the stroke volume is forwardly directed to the peripheral tissues and part of it is momentarily stored in the aorta and central arteries stretching the arterial walls and raising local BP. Part of the energy produced by the heart is diverted for the distension of arteries and is stored in the vessel walls. During diastole, the stored energy recoils the aorta, squeezing the accumulated blood forward into the peripheral tissues, ensuring a continuous flow. The efficiency of this function depends on the stiffness and geometry of the arteries. When the stiffness is low, arterial wall opposes low resistance to distension and the pressure effect is minimized. In hypertension, the arterial system is rigid and necessitates high pressure to be stretched to the same degree as in normotensives. A larger proportion of the stroke volume will flow through the arterial system and peripheral tissues mainly during systole with 2 consequences: intermittent flow and pressure, excessive flow and pressure pulsatility at the site of distal small resistance and short capillary transit time with reduced metabolic exchanges, altogether damaging target organs (Figure 3). The pulsatility of BP is further exaggerated by the phenomenon of wave reflection, as detailed below.

Measurement of Arterial Stiffness

Regional and local arterial stiffness can be measured directly, and noninvasively, at various sites along the arterial tree in humans. The measurement of pulse wave velocity (PWV) is generally accepted as the most simple, noninvasive, robust, and reproducible method with which to determine regional arterial stiffness. Carotid-femoral PWV (cfPWV), directly measured along the aortic and aortoiliac pathway, is the most clinically relevant because the aorta is responsible for most of the pathophysiological effects of arterial stiffness. cfPWV is measured using the foot-to-foot velocity method, and calculated as cfPWV=D (meters)/Δt (seconds), where D is the distance covered by the waves, usually assimilated to the surface distance between the 2 recording sites from various waveforms, and Δt is the time delay (or transit time). A large number of studies including a collaborative study in 16,867 subjects and patients, showed that age and BP were the main determinants of cfPWV, and that at a given age, cfPWV was higher in hypertensives than in normotensives.

Local arterial stiffness of superficial arteries (carotid, brachial, radial, femoral) can be determined noninvasively in humans using high-resolution echotracking devices. They have been developed to measure internal diameter, stroke change in diameter, and IMT with a high precision. For the calculation of wall properties, it is assumed that the cross section of an artery is circular and the arterial wall is homogeneous and uniformly load-bearing. The elastic properties of the artery as a hollow structure (its capacity to accommodate a certain volume of blood) are assessed through arterial distensibility, determined from the systolic–diastolic variations in arterial cross-sectional area and local PP (Figure 4). The elastic properties of the arterial wall material are estimated by the Young’s elastic modulus or incremental elastic modulus (Einc), which takes into account the thickness of the arterial wall. Young’s elastic modulus, expressed at a given arterial cross-sectional area and local PP (Figure 4), is the time delay (or transit time). A large number of studies, including a collaborative study in 16,867 subjects and patients, showed that age and BP were the main determinants of cfPWV, and that at a given age, cfPWV was higher in hypertensives than in normotensives.

Short-Term Changes in Arterial Stiffness in Hypertension

The understanding of arterial stiffening in hypertension necessitates to take into account the heterogeneity of the arterial wall structure. The molecular, cellular, and histological structure of the arterial wall is extremely complex. As far as arterial mechanics is concerned, the most important part of the arterial wall is the media. The basic element of the aortic and proximal elastic artery media is the lamellar unit or musculoelastic complex, first described by Wolinsky and Glagov in 1967, constituting of a single central layer of SMCs, which are separated by ECM from the elastic lamellae on either side. ECM contains mainly wavy collagen fibers and proteoglycans. The elastic lamellae are closely associated with thick curled collagen fibers containing types I, III, and V collagen. Numerous complex circumferentially oriented streaks of elastin protrude from the lamellae. The fibrillar elements of the matrix are highly connected to the VSMCs through dense plaques and
focal adhesion points, and the mechanical load is transduced in the cell through specific signaling pathways. In response, changes in the contractile state of the cell may profoundly influence the mechanical behavior of the artery, without significant changes in the wall composition.77

When BP is raised, there is a progressive loading (uncurling) and recruitment of stiff collagen fibers and distensibility decreases. This recruitment can operate during a few seconds or within 1 cardiac cycle where arterial stiffness increases from diastole to systole. From diastole to systole, BP and diameter rise in parallel (with a time-lag caused by viscosity of the wall material). The pressure–diameter or stress–strain relationship is curvilinear: artery is stiffer at high strain, but the increment in stiffness is larger at high strain than at low strain. Thus, the distensibility–pressure and compliance–pressure curves are curvilinear with negative slopes (Figure 4). The Young’s elastic modulus-circumferential wall stress curve is also curvilinear, with a positive slope (Figure 5). In patients with essential hypertension, the distensibility–pressure curves are shifted either toward higher BP levels at the site of the carotid artery or upward at the site of the radial artery but not downward compared with age- and sex-matched normotensives (Figure 4). Similarly, in patients with essential hypertension, the Young’s modulus-stress curves are shifted toward higher BP levels at the site of the carotid artery or upward at the site of the radial artery but not downward compared with age- and sex-matched normotensives (Figure 4). The recruitment of stiff collagen fibers and distensibility decreases. This recruitment can operate during a few seconds or within 1 cardiac cycle where arterial stiffness increases from diastole to systole. From diastole to systole, BP and diameter rise in parallel (with a time-lag caused by viscosity of the wall material). The pressure–diameter or stress–strain relationship is curvilinear: artery is stiffer at high strain, but the increment in stiffness is larger at high strain than at low strain. Thus, the distensibility–pressure and compliance–pressure curves are curvilinear with negative slopes (Figure 4). The Young’s elastic modulus-circumferential wall stress curve is also curvilinear, with a positive slope (Figure 5). In patients with essential hypertension, the distensibility–pressure curves are shifted either toward higher BP levels at the site of the carotid artery or upward at the site of the radial artery but not downward compared with age- and sex-matched normotensives (Figure 4). Similarly, in patients with essential hypertension, the Young’s modulus-stress curves are shifted toward higher BP levels at the site of the carotid artery but not upward in middle-aged and older hypertensives (Figure 5). Only in young hypertensives are they shifted upward, indicating a stiffer wall material.

Long-Term Changes in Arterial Stiffness in Hypertension

With age and hypertension, the repeated mechanical stress induced by the local pulsatility induces biomechanical fatigue of the wall components in the load-bearing media of elastic arteries. This is associated with a loss of the orderly arrangement of SMC and ECM. Elastic fibers and laminae display thinning, splitting, fraying, and fragmentation.77,78 Degeneration of elastic fibers is associated with an increase in collagenous material and in ground substance and often with deposition of calcium in this and in degenerate elastic fibers. Any alteration in collagen and elastin production and molecular repair mechanisms can theoretically change arterial elasticity.77,79

The relative content of collagen and elastin is controlled by a dynamic process of production and degradation, which acts at a low rate in physiological steady state condition. During disease process, degradation occurs through collagenases and elastases, produced by inflammatory cells such as macrophages and polymorphonuclear neutrophils, and gelatinase activation (matrix metalloproteinase-2 and matrix metalloproteinase-9), and contributes to altered mechanical properties.

In patients with essential hypertension, it has been largely demonstrated that large artery stiffness is elevated in response to the increased loading of stiff wall materials, such as collagen, by high levels of BP. However, controversy remains as to whether arterial stiffness is also increased in hypertension because of the biomechanical fatigue of wall components in

![Figure 4. Mean distensibility–pressure curves determined during the cardiac cycle in normotensive (NT) subjects and age- and sex-matched essential hypertensive (HT) patients. A, Common carotid artery; 14 NT and 15 HT. (Adapted with permission from Laurent et al45); B, Radial artery; 22 NT and 25 HT. The curve was significantly shifted upward in HT (P<0.05) (Adapted with permission from Laurent et al46). Results are presented as mean±SEM.](https://circres.ahajournals.org/doi/figure/10.1161/CIRCRESAHA.115.306148)

![Figure 5. Mean carotid artery elastic modulus-stress curves in normotensive (NT) subjects and age- and sex-matched essential hypertensive (HT). Analysis according to tertiles of age: 13 younger NT (open square), 13 middle-aged NT (mid NT, open circle), 13 older NT (open triangle); 34 younger HT (closed square), 34 middle-aged HT (mid HT, closed circle), and 34 older HT (closed triangle). Values are expressed as mean±SEM. The Einc-stress of the HT curve on the NT curve in the tertile of older patients. The same overlap was observed in middle-aged HT and NT. However, the Einc-stress curve of younger HT was shifted upward (P<0.001), with an overlap of the HT curve on the NT curve in the tertile of older patients. The same overlap was observed in middle-aged HT and NT. However, the Einc-stress curve of younger HT was shifted upward (P<0.001), with an overlap of the HT curve on the NT curve in the tertile of older patients.](https://circres.ahajournals.org/doi/figure/10.1161/CIRCRESAHA.115.306148)
response to the repeated pulsatile stress or additional mechanisms which are described below. Although clinical studies showed that aging and high BP stiffens the aorta at any given BP level, patients with essential hypertension surprisingly did not display any stiffening of the carotid artery wall compared with age-matched normotensives. In fact, only young essential hypertensives had increased stiffness of the wall material. The distensibility–pressure curves of hypertensive patients and animals were shifted toward higher levels of BP, and a large part of the curve overlapped that of normotensive subjects and animals. However, no significant downward shift of the distensibility–pressure curve was observed as it could have been expected if hypertension were associated with changes in the microconstituents of the arterial wall material (Figure 4). Only in young hypertensives were they shifted upward, indicating a stiffer wall material (Figure 5). The roles played by lumen enlargement and wall thickening in this adaptive mechanism are discussed below.

A large number of molecular components can influence the stiffness of the arterial wall, depending on associated cardiovascular risk factors and disease. For instance, the activation of the renin–angiotensin system can participate to structural alteration of the arterial wall. The chronic activation of systemic and local renin–angiotensin system promotes VSMC proliferation, low-grade inflammation, and increase in collagen content and advanced glycation end products formation. Low-grade inflammation may be variably associated with infiltration of VSMC, macrophages, and mononuclear cells; increased content of matrix metalloproteinases and cytokines; mediasl lactifications; changes in proteoglycan composition and state of hydration; and cellular infiltration around the vasa vasorum leading to vessel ischemia. Abnormal, stiffer collagen molecules can result from enzymatic glycation-cross-linking, for instance during impaired glucose tolerance and diabetes mellitus. These irreversible cross-links form advanced glycation end products. Tyson et al have suggested a sequence of molecular events in vascular calcification beginning with the loss of expression by VSMCs, of constitutive inhibitory proteins, and ending with expression by VSMCs and macrophages of chondrocytic, osteoblastic, and osteoclastic-associated proteins that orchestrate the calcification process.

The above mechanisms are variably associated in patients with essential hypertension, depending on the associated cardiovascular risk factors or disease. In secondary forms of hypertension, such as primary aldosteronism or renovascular hypertension, arterial stiffness is due either to the fibrotic effect of high aldosterone levels or to the continuous activation of the renin–angiotensin system.

### Stiffness Gradient and Wave Reflection

The understanding of the mechanisms leading to wave reflection and augmented central PP in hypertension needs to take into account the heterogeneity of elastic properties along the arterial tree, which creates a stiffness gradient. In normotensive subjects, the distensibility of conduit arteries decreases from upstream elastic proximal large arteries to downstream stiffer distal medium size arteries (Figure 6). Although all of the large artery segments have 3 layers (intima, media, and adventitia), large proximal elastic arteries and medium size distal muscular arteries differ in the relative amount of VSMCs and ECM (especially elastin) in their media, which plays the most influent role in elastic properties. In humans, PWV increases from 4 to 5 m/s in the ascending aorta to 5 to 6 m/s in the abdominal aorta and then 8 to 9 m/s in the iliac and femoral arteries. In middle-aged normotensive subjects, the cross-sectional distensibility, assessed with echotracking systems, decreases from 40 kPa−1×10−3 in the thoracic aorta to 15 to 25 kPa−1×10−3 in the carotid and brachial arteries, 10 to 15 kPa−1×10−3 in the common femoral artery, to 5 kPa−1×10−3 in the radial artery. The media of large proximal artery contains both VSMCs and many elastin lamellae, whereas the media of medium size distal artery is less elastic and the VSMCs prevail. The mismatch of impedance between elastic proximal arteries and stiffer medium size muscular arteries can generate partial wave reflections, far from the small resistance arteries. Partial reflections limit the transmission of pulsatile energy to the periphery and protect the microcirculation. In hypertensive patients, aortic stiffness increases and the stiffness gradient disappears (Figure 6). Less wave reflections are generated. The pulsatile pressure is not sufficiently dampened and is transmitted, damaging the microcirculation.

### Arterial Wall Hypertrophy and Stiffness

According to physics laws, any increase in wall thickness should increase arterial stiffness for a given BP level because of the juxtaposition of materials having identical mechanical properties. Surprisingly, we and others found that hypertrophy, observed in hypertensive, was accompanied by a reduced stiffness of the wall material (Young’s elastic modulus) and a normal stiffness of the artery considered as a whole (1/cross-sectional distensibility) when compared at a given BP or wall stress. Similar findings were observed in SHRs and stroke-prone SHRs at the site of the carotid artery and the abdominal aorta, when hypertensive strains were compared with Wistar-Kyoto rats. This means that the
hypertension-induced wall thickening is not associated with an increased stiffness in patients with essential hypertension and rat models of hypertension, but rather with a rearrangement of the arterial wall material leading to the mechanical adaptation of the arterial wall to higher levels of BP. Several mechanisms could redistribute the mechanical load toward elastic materials, including a higher number of cell-matrix attachments (fibronectin/α5β1 integrin complexes and elastin/VSMC connections), smaller fenestrations of the internal elastic lamina, and increased VSMC tone. The role played by increased VSMC tone has been suggested from gene expression profile studies, theoretical model of 3 dimensional arterial mechanics, and atomic force microscopy and demonstrated in knockout mice with deletion of the VSMC serum response factor, a major transcription factor regulating smooth muscle genes involved in maintenance of the contractile state. Altogether, these results suggest that not only the organization and content of the ECM but also the changes in the structural and functional properties of the VSMCs can influence arterial stiffness.

**Arterial Stiffness and Remodeling, Wave Reflection, and Central BP**

Several models of the circulation have been proposed to estimate the total compliance of the arterial system. Particularly, in the Windkessel model, the arterial system is compared to a simple distensible tube which terminates at the peripheral arteries than central arteries, as seen above. These assume that the velocity with which pressure wave travels along the arterial tree, with stiffer peripheral arteries than central arteries, the so-called amplification phenomenon. This phenomenon is exaggerated by hypertension.

Propagative models are thus more often used than Windkessel models to describe the circulatory system. They consist of a simple distensible tube which terminates at the peripheral resistance, but whose distributed elastic properties permit generation of a pressure wave which travels along the tube. These assume that the velocity with which a pulse wave travels along a given artery has a finite value. Bramwell and Hill in 1922 derived the Moens–Korteweg equation (ie, $c = \sqrt{Eh/2R}$), where $c$ represents wave speed, $E$ is the Young’s modulus in the circumferential direction, $h$ is wall thickness, $R$ is radius, and $\rho$ is the density of fluid) as $c = \sqrt{Vx\rho \times dP}$, where $dV$ is the change in arterial volume ($V$) and $dP$ is the change in pressure driving the change in volume. This equation is currently widely used in clinical research and clearly illustrates the facts that the propagation of the pulse wave is inversely related to the distensibility of the arterial tube, expressed as $dV/V \times dP$.

O’Rourke and others have also suggested that because the tube’s end has a high level of resistance, waves are reflect and retrograde waves are generated. The stiffness gradient between large elastic arteries and medium size muscular arteries, together with the geometric taper, local arterial branching, and lumen narrowing of medium size arteries, creates an impedance mismatch causing partial reflections of forward pressure waves travelling back to the central aorta (reflected wave). In addition, the geometry, number of arterioles, and the architecture of the microvascular network all play an important role in wave reflection. With hypertension-induced arterial stiffening, the reflected wave travels more rapidly along the arterial tree. Thus, both small and large arteries contribute to early reflected waves which arrive in early systole, superimpose on the forward wave, and boost the systolic pressure further. These mechanisms explain why the structural and functional changes of large and small arteries in hypertension cause a premature return of reflected waves in late systole, increasing central PP, thus systolic BP.

In peripheral arteries, wave reflections can amplify the pressure wave because reflection sites are closer to peripheral sites than to central arteries, and PWV is higher in a peripheral stiffer artery than in a central elastic artery. The net result is that the amplitude of the pressure wave is higher in peripheral arteries than in central arteries, the so-called amplification phenomenon. This phenomenon is exaggerated by hypertension. It explains why it is inaccurate to use brachial PP as a surrogate for aortic or carotid PPs, particularly in young subjects in whom brachial PP overestimates central PP, and why central SBP and PP are more related to organ damage than brachial SBP and PP, as will be described below.

**Large/Small Artery Cross-Talk in Hypertension**

In essential hypertension, small and large artery alterations are closely interdependent. A temporal relationship is difficult to establish, and a cross-talk, by which small artery alterations influence larger artery phenotype, and conversely large artery alterations influence small artery phenotype, is more likely than a linear sequence.

**Large/Small Artery Cross-Talk and Central Pulsatility**

A cross-talk between small and large artery can be exemplified by the following vicious circle of small/large artery damages (Figure 7), which can be described from any step. Each step refers to pathophysiological changes described above. When necessary, additional evidence is detailed. For instance, we can start the description from small artery damage:

**Step 1:** Vasoconstriction, impaired vasodilatation, increased wall-to-lumen ratio associated with reduced lumen diameter, and rarefaction of small arteries are major determinants of the increase in total peripheral resistance and mean BP

**Step 2:** The higher mean BP in turn increases large artery stiffness, through the loading of stiff components of the arterial wall at high BP levels.

**Step 3:** The increased large artery stiffness leads to high central systolic and PPs. In addition, structural alterations in small resistance arteries contribute to increase in the amplitude of wave reflection, which acts synergistically with the increased PWV to ultimately rise central systolic and pulse PPs. These relationships are exemplified by the fact that, in...
hypertensive patients, media-to-lumen ratio of subcutaneous small resistance arteries and cPWV are both independent determinants of central SBP.

Step 4: The increased central BP pulsatility is correlated with damage of small resistance arteries, ie, increased media-to-lumen ratio of subcutaneous small resistance arteries. This has initially been reported in hypertensive animals, and then in hypertensive patients with brachial PP and more recently with central systolic and PPs measured with applanation tonometry. Interestingly, the wall-to-lumen ratio of retinal arteries is significantly correlated with 24-hour systolic BP.

Steps 5 and 1: Increased media-to-lumen ratio of subcutaneous small resistance arteries, which is associated with reduced lumen diameter, represents the largest part of the structural part of increased total peripheral resistance, leading to a rise in mean BP, and so continuing the vicious circle. This pathophysiological approach can be completed at several levels:

1. The hypertension-induced remodeling of the vasa vasorum contained in the periaortic fat of the adventitia can reduce the vasa vasorum flow and impair the nutrition of the outer layers of the thoracic aorta, leading to increased aortic stiffness. Not only is arterial stiffening a consequence of the rise in mean BP but also arterial stiffening may be the determinant of elevated systolic BP on the long term. Longitudinal assessment of the temporal relationship between carotid aortic stiffness on the one side and incident hypertension on the other side suggests a precursor role of arterial stiffening in future altered systolic hemodynamic load.

2. We previously detailed how the mechanical load applied on the arterial wall was shifted toward more elastic material during essential hypertension and suggested that this can be viewed as a means to compensate for the deleterious effects of wall hypertrophy and avoid excessive arterial stiffening at high BP levels. This compensative mechanism may also reduce the stiffness gradient between proximal and distal medium-sized arteries, and thus reduce wave reflection and central PP.

Central Pressure Pulsatility and Target Organ Damage
As detailed above, the small/large artery cross-talk exerts a synergistic effect on target organs, mainly through the excess of pulsatile energy which is delivered either as central peak BP (systolic) or as PP. Recent findings are consistent with the hypothesis that central systolic and PPs are the most damaging components of the BP load on target organs. Their elevations have been found to exhibit a closer correlation with hypertensive target organ injury than either systolic and pulsatile components measured at the brachial artery or the steady component (mean BP).

Cardiac Damage
As far as the myocardium is concerned, a higher correlation has been observed with central SBP and PP than with brachial SBP and PP for left ventricular hypertrophy, systolic dysfunction, diastolic dysfunction, and left atrial enlargement and new onset of atrial fibrillation. Both large and small artery damages contribute to the pathophysiology of cardiovascular diseases. For instance, central SBP increases the load on the left ventricle, increasing myocardial oxygen demand. In addition, arterial stiffness is associated with left ventricular hypertrophy, a known risk factor for coronary events. The increase in central PP and the decrease in diastolic BP may directly cause subendocardial ischemia. Decreased large epicardial coronary vascular tree perfusion during diastole is a consequence of enhanced central pulsatility and leads to decreased coronary flow reserve. Rarefaction and remodeling of intramyocardial coronary artery, left ventricular hypertrophy, and left ventricular diastolic dysfunction further contribute to microcirculatory flow reserve reduction, impaired tissue perfusion, and susceptibility in ischemia during high metabolic and oxygen demand. Epicardial coronary atherosclerosis exaggerates the deleterious effects of above damages and contribute to the pathogenesis of ischemic heart disease.

Brain Damage
Large/small artery damage can increase the risk of ischemic stroke, white matter lesions, lacunar infarcts, and cognitive decline through several mechanisms. An increasing body of evidence suggests that high PP transmitted into cerebral arteries can lead to small cerebral artery remodeling with progressive encroachment of the arterial lumen aimed at protecting the microcirculation from pulsatile stress. The cerebral circulation (together with the kidney) is particularly susceptible to pressure damage because this is a torrential circulation with minimal vascular resistance, therefore mean and PPs are easily transmitted from the aorta to small cerebral (and renal) arteries. Two studies reported that an increased arterial pulsatility because of large artery stiffening can be transmitted to cerebral small vessels and associated with white matter lesions. Carotid flow pulsatility index, measured either with transcranial Doppler in the middle cerebral artery or with extracranial Doppler in the CCA, as well as carotid PP and cPWV, were associated with increased risk for microvascular...
structural brain damage, such as silent subcortical infarcts or white matter lesions,119,120 and lower scores in various cognitive domains.120 Carotid stiffness has also been used as proxy for middle-size cerebral arterial stiffness and reported to be associated with increasing large white matter hyperintensity volume, independent of vascular risk factors and carotid plaque.116

In hypertension, the inward remodeling of small cerebral artery and associated increased myogenic tone impair vaso-motor reactivity, limit the autoregulation of cerebral blood flow, and increase susceptibility to focal ischemia when BP is transiently and acutely low.121 Patients with exaggerated visit-to-visit variability of BP, namely SBP, are at increased risk of stroke,122 which suggests that repeated episodes of hypoperfusion and microvascular ischemia, that are more likely in those patients, could favor tissue damage and stroke.

Finally, a high central PP influences arterial remodeling not only at the site of the intracranial arteries but also in extracranial arteries, increasing carotid wall thickness, leading to the development of plaques.123

Renal Damage
We explained above how impaired myogenic tone of the renal circulation reduces the autoregulation capacity and increases the baro-trauma because of high systolic BP, leading to glomerular injury. Thus, in hypertensive patients with type 2 diabetes mellitus, even modest increases in systemic BP are transformed into higher pulsatile energy transmitted to the kidney, with higher dissipation in the microcirculation, hyperfiltration, and glomerulosclerosis. Clinical investigation is consistent with this pathophysiological approach. Significant relationships have been demonstrated between brachial PP and either glomerular filtration rate or microalbuminuria124; between arterial stiffness and either glomerular filtration rate119,125 or urinary albumin125; between carotid stiffness and glomerular filtration rate126; and between central PP and incident end-stage renal disease.62 Although not all these relationships are independent of confounding factors, there is a large amount of evidence for linking the pulsatility of BP to renal damage.

Cardiovascular and Renal Outcome
Because the small/large artery cross-talk exerts a synergistic damaging effect on target organs, it is not surprising that arterial stiffness,67-70,126 central systolic and PPs,127,128 and media-to-lumen ratio of small resistance arteries129 have independent predictive value for cardiovascular (CV) events and renal complications in hypertensive patients. Several reviews4,66,99,108 have already addressed this issue.

Prognostic Value and Clinical Usefulness of Arterial Stiffness and Central BP
Arterial stiffness has a particular status. Its measurement is recommended by the 2007130 and 2013131 European Society of Hypertension-European Society of Cardiology Guidelines for the Management of Hypertension. The largest amount of evidence has been given for aortic stiffness, measured through cPWV which is considered as gold standard.66 A large number of studies showed the independent predictive value of cPWV for all-cause and cardiovascular mortality, fatal and non fatal coronary events, and fatal strokes not only in patients with uncomplicated essential hypertension but also in patients with type 2 diabetes mellitus or end-stage renal disease, in elderly subjects and in the general population.67-70,126 In addition, aortic stiffness proved to complete several criteria (proof of concept, prospective validation, incremental value, and clinical utility) for being considered as a true surrogate end point for CV events, according to a statement from the American Heart Association.132 There is still a need for studies comparing aortic stiffness-guided therapeutic strategies with classical guidelines-guided strategies for preventing CV events, to fulfil the fifth criteria (clinical outcomes).133

We detailed above how the small/large artery cross-talk could exert a synergistic effect on target organs, mainly through the excess of pulsatile energy which is delivered as central PP. As expected, central PP has predictive value for CV events.62,127,128 However, the predictive value of central PP for CV events should remain significant after adjustment to classical CV risk factors, and particularly brachial PP. But this has not been consistently demonstrated. In a recent meta-analysis,127 only a marginal superiority of central PP over brachial PP for predicting CV events was observed, and there was no superiority of central SBP over brachial SBP. Additional studies, not included in the meta-analysis, also failed to show higher predictive values of central PP compared with brachial PP.126,134 There is an ongoing controversy on whether the lack of higher predictive value of central BP compared with brachial BP is related to the method used for central BP measurement135 or reflects a true pathophysiological issue. Thus, the 2007 and 2013 European Society of Hypertension-European Society of Cardiology Guidelines for the Management of Hypertension130,131 considered that although the measurement of central BP and augmentation index was of great interest for mechanistic analyses in pathophysiology, pharmacology, and therapeutics, more investigation was necessary before recommending their routine clinical use.

Conclusions
The main features of the arterial system in essential hypertension include small and large artery remodeling, with associated functional changes. The geometric and structural changes of small arteries include eutrophic inward remodeling and rarefaction in the microcirculation. They lead to an increase in the structural part of vascular resistance, exaggerate the vasoconstrictive response to various agents, and impair the autoregulation of blood flow to organs. The geometric and structural changes of large artery are variably associated with remodeling and stiffening, depending on the arterial site. These changes play a major role in the generation of pressure wave reflection and augmentation of systolic and PPs. The small/large artery cross-talk exerts a synergistic effect on target organs, mainly through the excess of pulsatile energy which is delivered either as central systolic or PPs. The main parameters of large and small artery alterations, ie, arterial stiffness, central systolic and PPs, and media-to-lumen ratio of small resistance arteries, have independent predictive value for CV events and renal complications in patients with hypertension.
Sources of Funding
This review was funded by INSERM, University Paris-Descartes, and Assistance Publique-Hôpitaux de Paris.

Disclosures
None.

References


Stiffness of the carotid arterial wall material is not increased in patients with essential hypertension. Arterioscler Thromb. 1994;14:1223–1231.


Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991;114:345–352.


Fesler P, Safar ME, du Callar G, Ribstein J, Minnan A. Pulse pressure is an independent determinant of renal function decline during treatment of


The Structural Factor of Hypertension: Large and Small Artery Alterations
Stéphane Laurent and Pierre Boutouyrie

Circ Res. 2015;116:1007-1021
doi: 10.1161/CIRCRESAHA.116.303596
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/116/6/1007

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/