Large conduit arteries in hypertension: role of the vascular renin-angiotensin system

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LARGE ARTERIES such as the carotid, coronary, and renal arteries are traditionally thought of as passive conduits whose principal function is to conduct and distribute cardiac output to various tissues. Conduit arteries represent a low resistance system that is not thought to be involved with blood flow regulation. Most of the research in hypertension has focused on the small arteries and resistance arterioles. However, our recent knowledge of the pathology and physiology of the large arteries suggests that these vessels may play an important role in the pathophysiology of hypertensive vascular disease. For example, large arteries have an important buffering function to phasic changes in pressure. The distensibility of these vessels affects the impedance to ventricular ejection, which is important in determining end-systolic ventricular wall stress, an important factor in the pathophysiology of cardiac hypertrophy and failure. Furthermore, large vessels are prone to develop arteriosclerosis, which is the major cause of cardiovascular complications.

Emerging evidence indicates that large arteries are not passive conduits but are active vessels that are responsive to vasoactive substances such as angiotensin II. Experiments in vivo and in vitro have demonstrated that femoral, coronary, and carotid arteries contract in response to norepinephrine, prostaglandin $F_{2\alpha}$, and angiotensin, and relax in response to acetylcholine, prostacyclin, nitroprusside, atrial natriuretic factor, etc. Recent reports of the existence of a local renin-angiotensin system in blood vessel walls, especially in large arteries, have raised the possibility that vascular function may be regulated by local production of angiotensin II independent of the circulating levels. Indeed, recent experimental and clinical studies have demonstrated that blockade of angiotensin II production by angiotensin converting–enzyme inhibitors increased the compliance of these large arteries. Taken together, these data raise new and important questions in the control of the functions of the large arteries.

The purpose of this brief review is to examine the role of large arteries in hypertension and to elucidate the contribution of the vascular renin-angiotensin system to the pathophysiology and therapy of hypertension.

Importance of large arteries in hypertension. It is well recognized that the complications associated with hypertension are frequently the result of arteriosclerotic vascular disease. Large vessels are particularly prone to injury because of the continued exposure to high pulsatile pressure and shear stress. The thickness of these vessels also increases the potential of increased lipoprotein deposition. Endothelial dysfunction or denudation that results from hemodynamic injury and/or metabolic imbalances can elicit a sequence of responses in the blood vessel wall that eventually lead to formation of the arteriosclerotic plaque. Thus, the adaptive properties of large artery to changes in pressure and shear stress may be important deterrents to vascular injury. In other words, the viscoelastic and compliant properties of these vessels provide a buffer to abrupt increases in pressure. Factors that decrease arterial compliance may impair the adaptive response and increase the potential of vascular injury. Humoral
substances such as norepinephrine and angiotensin II have been shown to increase the contractile state of the large arteries. It is conceivable that the increased atherosclerotic complications seen in the hypertensive animal or man may be partly related to the changes in vascular properties in response to excess catecholamine and stress. Conversely, factors that increase compliance of the large arteries such as therapy with converting-enzyme inhibitors may reduce hypertensive vascular injury.

Although large arteries have not been traditionally thought to be involved with the distribution of blood flow, recent evidence suggest that they may play such a role. Blood flow is the product of flow velocity and the cross-sectional area of the artery.\(^1\)\(^\text{-}\)\(^4\) Thus, an increase in blood flow may be related to an elevation of either of these factors or both. In regional vascular beds such as the cerebral and coronary circulations, autoregulation of blood flow results from adaptive modification in the caliber of small arteries.\(^5\) In the presence of stenosis of large arteries, the small arteries and arterioles are maximally dilated. Under these conditions, the increase in large artery caliber may be an important factor in maintaining flow during antihypertensive treatment.\(^6\) Indeed, it has been suggested that the dilating effect of converting-enzyme inhibitor on the carotid and cerebral arteries may contribute greatly to the maintenance of adequate cerebral perfusion during the initiation of antihypertensive treatment.\(^6\),\(^7\)

In addition to their conduit function, large arteries have a buffering function causing the phasic flow of cardiac output to be translated into a continuous flow at the peripheral level. In this regard, the viscoelastic properties of the arterial wall play an important role,\(^8\) enabling part of the stroke volume to be stored in the arterial wall during systole and to flow toward the periphery during diastole. In patients with essential hypertension, the buffering function of large arteries is modified since arterial compliance is reduced.\(^9\) It has been traditionally believed that decreased compliance in hypertension is a passive phenomenon resulting from the hydraulic effect of chronic elevation of the distending pressure. Recent studies show that this is not always the case.\(^10\) For the same levels of mean arterial pressure, different levels of arterial compliance and pulse pressure may be observed. For instance, arterial compliance is lower and pulse pressure is higher in older as compared with younger hypertensive patients for the same level of mean arterial pressure.\(^11\),\(^12\) Vasoactive substances such an angiotensin and norepinephrine may contribute to these changes in arterial compliance in hypertension.\(^1\)\(^-\)\(^4\) As a corollary, antihypertensive agents that influence the activity of these vasoactive substances may produce different responses in arterial compliance.

It has been suggested that cardiac hypertrophy is a passive consequence of the chronic elevation of blood pressure. This assumption has been recently reexamined on the basis of several observations. First, cardiac hypertrophy may be observed in patients with nearly normal blood pressure, as in those with borderline and mild hypertension.\(^23\) Second, in patients with sustained essential hypertension, the correlation coefficient of the relationship between cardiac mass and blood pressure is relatively low.\(^24\)-\(^26\) The development of cardiac hypertrophy is an adaptive response to increased afterload. End-systolic stress or arterial impedance rather than blood pressure per se are determinants of afterload.\(^1\)\(^-\)\(^4\) From the studies of arterial impedance, it appears that cardiac hypertrophy is influenced not only by the level of blood pressure and total peripheral resistance, but also by the state of arterial distensibility.\(^27\),\(^28\) Indeed, cardiac hypertrophy and hypertension is strongly correlated to pulse-wave velocity and distensibility. Furthermore, cardiac hypertrophy is better correlated to systolic than to diastolic pressure,\(^28\) suggesting that reduced arterial distensibility and compliance may influence the development of cardiac hypertrophy through a disproportionate increase in systolic pressure.\(^28\) Further evidence that the relationship between blood pressure and cardiac hypertrophy is oversimplified is derived from the data on regression of cardiac hypertrophy associated with antihypertensive therapy. Indeed, drugs that fail to lower impedance and/or drugs that activate sympathetic nervous system tend to have little effect with regard to regression of cardiac hypertrophy.\(^27\),\(^28\) In contrast, converting-enzyme inhibitors, which increase arterial distensibility and lower systolic pressure and end-systolic stress, appear to facilitate regression of cardiac hypertrophy.\(^27\)-\(^29\)

In the presence of congestive heart failure, afterload reduction has become an established therapeutic modality. In this condition, activation of angiotensin and norepinephrine can increase afterload, resulting in increased wall stress and aggravation of heart failure.\(^30\),\(^31\) Angiotensin converting–enzyme inhibitors are particularly efficacious in the treatment of this disorder.\(^32\),\(^33\)

**Concepts and determinants of arterial hemodynamics.** Studies of arterial hemodynamics in humans are usually based on invasive recordings of pressure and flow in the aorta. Thus, the impedance spectrum of large
arteries may be evaluated, enabling the simultaneous investigation of the resistance, capacitance, and inertia of the arterial system.1-4 In simpler models, only the elastic component of the systemic circulation can be taken into account.19 However, determination of arterial impedance, although possible, still poses many practical difficulties.

Over recent years, improved pulsed Doppler methods have become available for transcutaneous investigations of intact superficial large arteries in normal and hypertensive subjects.34, 35 For this purpose, two features of the apparatus are necessary: a range-gated system and a double transducer probe. With these techniques, it is now possible to measure simultaneously the internal diameter and the cross-sectional area of straight superficial arteries, such as the brachial and the common carotid arteries. Adequate validations have been performed in vitro and in vivo.34, 35

The conduit function of the large artery may be studied from the determination of arterial diameter and blood flow velocity. Assuming a cylindrical model of the artery, the arterial cross-sectional area can be estimated from the measured diameter. Blood flow can be calculated as the product of the cross-sectional area and blood flow velocity. Resistance is calculated as the ratio between mean arterial pressure and brachial blood flow. Thus, the pulsed Doppler system provides important information about the degree of arterial dilation: (1) dilation of small arteries is indirectly inferred from the calculation of vascular resistance, and (2) dilation of large arteries is evaluated directly from the large artery diameter measurement.

The buffering function of large arteries may be investigated from the determination of arterial compliance, which is the slope of the pressure-volume relationship within the artery, i.e., the ratio between the change in volume (dV) divided by the change in pressure (dP).1-4 Propagative and nonpropagative models of the forearm circulation have been described for the determination of compliance. The latter is evaluated from a simple first-order model of the brachial artery tree (Windkessel model), with the dampening effect of the vessel assumed.19, 20 The former requires the simultaneous determination of arterial diameter and pulse-wave velocity (PWV) with the use of classic noninvasive techniques.36 Thus, arterial compliance may be calculated as the ratio between the cross-sectional area of the artery and pPWV2, p being the blood density assumed as a constant (table 1). This ratio indicates that arterial compliance, when expressed per unit length, is the quotient of atrial distensibility (dC/dP/V, where C is compliance and V is volume) divided by arterial volume, calculated as (3.57/PWV)2 according to the Bramwell and Hill formula.1-6

When the effect of a given antihypertensive drug on the large arteries is studied, it must be recalled that the decrease in blood pressure per se modifies the geometry of the large artery as a result of the viscoelastic properties of the arterial wall. According to the experiments of Hallock and Benson,38 the decrease in blood pressure is accompanied by a passive decrease in arterial diameter and volume, an increase in arterial compliance (dV/dP), and a proportional decrease in systolic and diastolic pressures. Thus, if an antihypertensive agent acts specifically on the wall of a given large artery through an effect on arterial smooth muscle tone, one or several of the following modifications may be observed: (1) a nonproportional decrease in systolic and diastolic pressures, (2) a change in compliance of distensibility unrelated to a level of blood pressure, and (3) an increase in arterial diameter despite the occurrence of a reduction in blood pressure.

Arterial diameter and compliance can be influenced by intrinsic properties of the blood vessel wall as well as various vasoactive mechanisms. Indeed, arterial stiffness can be the result of medial hypertrophy and proliferation, increased collagen content, or calcific arteriosclerosis of the blood vessel.1-4 It has been known for a long time that adrenergic and angiotensin receptors exist on large arteries.5, 6 Angiotensin II and α1-adrenergic agonists (methoxamine, phenylephrine) can result in enhanced contraction of aorta and other large arterial strips.5, 6 Other vasoactive substances have also been shown to influence the contractile state of the large blood vessel. Recently, the endothelium has been implicated to play an active role in determining the state of vascular smooth muscle contractility.39, 40 Furthermore, heterogeneity of responses between different blood vessels to various vasoactive substances has also been reported. Thus, the blood vessel is an organ that is biosynthetically active, producing various local vasoactive substances that can influence vascular function by an autocrine or a paracrine mechanism.41 Accordingly, one would anticipate that agents that influence the activity of these local vasoactive substances may influence blood vessel function (such as distensibility and diameter). An emerging area of great interest to vascular biologists and pharmacologists is the vascular renin-angiotensin system.

**Vascular renin-angiotensin system.** Angiotensin II receptors are widely distributed throughout the vascular tree from resistance arterioles to the aorta.1 It is well known that systemic administration of angiotensin can result in blood pressure elevation due to increased
systemic vascular resistance. Angiotensin also produces contractions in the aortic strip or ring as well as in isolated femoral, carotid and coronary arteries.\textsuperscript{5, 8} Indeed, infusion of angiotensin into various vascular beds has generally been shown to cause vasoconstriction in these vascular beds.

In the last few years, renin-like enzymes have been described in a variety of tissues, including blood vessels such as aorta, carotid, and coronary arteries, and in the veins.\textsuperscript{7, 8} Several investigators have demonstrated that the renin-like activity in the aorta persists for many hours in nephrectomized rats after plasma renin activity is no longer detectable.\textsuperscript{42, 43} Aguirela et al.\textsuperscript{44} were able to measure immunoreactive angiotensin II in the plasma of rats 24 hr after bilateral nephrectomy, at which time plasma renin activity was undetectable. These data suggest that angiotensin II production may occur at sites outside the plasma and that the peptide is released from the tissue of production into the circulation. The concept of local synthesis of angiotensin II in vascular wall was suggested by the data of Swales and Thorston,\textsuperscript{45} who reported that the amount of angiotensin antiserum required to inhibit exogenous angiotensin effect in sodium-loaded rats was in marked excess of that predicted. These investigators believed that the data could not be explained solely by alterations in the angiotensin receptor or sensitivity, and they interpreted the findings as suggesting local synthesis of angiotensin II in the vascular wall, which influenced the response to antiserum.

Renin-like activity in the blood vessel wall has been shown to be primarily derived from immunoreactive renin based on the ability of antirenin antibody to neutralize its activity and the presence of positive immunostaining by antirenin.\textsuperscript{46} Angiotensinogen mRNA has been detected in the blood vessel wall (in the perivascular fat and in the medial smooth muscle).\textsuperscript{47} Angiotensin-converting enzyme and immunoreactive angiotensins have also been demonstrated throughout the vasculature.\textsuperscript{48} Thus, the blood vessel wall contains the essential components of the renin-angiotensin system. The origin of vascular renin is a subject of some debate.\textsuperscript{49} Loudon et al.\textsuperscript{50} demonstrated that plasma renin can be taken up by the blood vessel where it exerts a local effect in generating angiotensin. We have reported that prorenin may be absorbed into and activated by endothelial cells.\textsuperscript{51} In addition to uptake of circulating renin there is also evidence of local renin synthesis based on in situ hybridization histochemistry and experiments on cultured vascular cells.\textsuperscript{9, 10}

The observations that angiotensins may be produced locally in the blood vessel\textsuperscript{9, 10, 50} may have important physiologic, pathophysiologic, and pharmacologic implications. Vascular renin angiotensin may accumulate in the blood vessel wall in concentrations that exceed those in plasma. Local angiotensins may exert a variety of autocrine or paracrine influences on vascular tone or on the growth of the blood vessel.\textsuperscript{41} Local angiotensin may stimulate vasoconstriction by activating its receptors on vascular smooth muscle cells. Accumulation of angiotensin in the region of noradrenergic nerve endings (especially in the outer medial layers) may increase sympathetic vascular tone by facilitating catecholamine release from nerve endings.\textsuperscript{52–54} Vascular angiotensin may also influence endothelial prostacyclin synthesis as well as endothelium-derived relaxant factor release, which may result in vasodilation.\textsuperscript{55} Recently, Yamaguchi and Nishimura\textsuperscript{56} observed that Sar\textsuperscript{1} Val\textsuperscript{5} angiotensin II may relax chick aorta by the release of an endothelial-derived relaxant-like factor.

The paracrine-autocrine influence of local angiotensin on blood vessel growth, e.g., hypertrophy and hyperplasia, should also be considered. First, angiotensin can influence blood vessel growth indirectly via its effect on norepinephrine release from noradrenergic nerve endings.\textsuperscript{50} The sympathetic nervous system plays an important role in vascular hypertrophy.\textsuperscript{57} Norepinephrine has been shown to be capable of inducing the growth of cardiac myocytes and stimulating the expression of proto oncogene c-myc.\textsuperscript{58} Its role in the stimulation of vascular myocyte growth remains to be established. Second, angiotensin may have a direct growth-promoting effect on vascular growth muscle cells. Campbell-Boswell and Robertson\textsuperscript{59} reported that angiotensin stimulated proliferation of cultured human vascular smooth muscle cells grown in serum. On the other hand, Geisterfer and Owen\textsuperscript{60} reported that in quiescent confluent aortic smooth muscle cells cultured in serum-defined free medium, angiotensin increased protein synthesis and cell mass without stimulating cell division. Regardless of the exact effect, the local angiotensin system may exert important trophic and growth-regulating influences on the blood vessel (large and small arteries) in hypertension.

Support for the concept that vascular renin-angiotensin system is activated in hypertension is derived from several lines of evidence. In various forms of experimental hypertension, aortic renin concentrations have been observed to be increased as compared with the levels in normotensive controls.\textsuperscript{61} In the spontaneously hypertensive rat, Asaad and Antonaccio\textsuperscript{62} reported that the concentration of aortic wall renin...
correlated with the level of blood pressure. Okamura et al. observed that aortic, mesenteric, and renal ACE activities were increasing during chronic two-kidney, one-clip renovascular hypertension in the rat, despite normal plasma renin activity. Indeed, angiotensin II generation appears to be accelerated in the aortic wall in these animals and the administration of converting-enzyme inhibitors/angiotensin II antagonists ameliorates the elevation in blood pressure. Vascular angiotensin II may influence large artery function through the direct activation of angiotensin II receptors in the smooth muscle cells. Alternatively, local angiotensin may influence blood vessel contractility by facilitating catecholamine release from noradrenergic nerve endings.

Evidence for angiotensin hyperreactivity in large arteries in human essential hypertension has been provided by clinical studies. It has been observed that converting-enzyme inhibitors (captopril and enalapril) cause a significant increase in arterial diameter in both the brachial and carotid arteries. With long-term enalapril therapy (up to 6 months), the diameter enhancement is maintained. In contrast, converting-enzyme inhibitors do not influence arterial diameter, blood flow, or indexes of arterial stiffness (as measured in the brachial artery) of normal healthy volunteers. This observation supports a contribution of vascular angiotensin rather than its serum counterpart in mediating the altered arterial compliance in hypertension since in both of these cited studies serum ACE activities were inhibited up to 95%.

In another study involving normal volunteers, high doses of the converting-enzyme inhibitor Perindopril were required to produce significant increases in arterial diameter and blood flow. In contrast, in hypertensive subjects, conventional doses of the converting-enzyme inhibitor influenced arterial hemodynamics. These findings were obtained in the presence of significant blood pressure reductions, suggesting that the mechanical effects of blood pressure were offset by the dilating effects of converting-enzyme inhibitor. Taken together, these results suggest that hypertensive subjects may have enhanced production of or sensitivity to local angiotensin.

Effects of converting-enzyme inhibitors and other antihypertensive agents on the conduit and buffering function of large arteries. Angiotensin converting–enzyme inhibitors (captopril, enalapril, and ramipril) cause arterial vasodilatation and induce an increase in flow velocity in the large artery. As mentioned above, these agents also increase cross-sectional area of the large arteries, which may play a role in the increase of blood flow. The quantitative contribution of the increase in arterial caliber to the flow increases in the carotid, cerebral, coronary, and renal circulations is unclear. In conditions associated with intense angiotensin II-mediated vasoconstriction of the renal arteries, such as hepatorenal syndrome and congestive heart failure, convertingenzyme inhibition and angiotensin II antagonism, in addition to their effect on the arterioles, have been shown to increase renal blood flow based on relaxation of the large and medium-sized arteries. Under conditions of large artery stenosis, an increase in large artery caliber may be an important factor in maintaining flow during converting-enzyme inhibition since the arterioles are maximally vasodilated. As mentioned, it has been suggested that the dilating effect of captopril on the carotid and cerebral arteries may contribute greatly to the maintenance of adequate cerebral perfusion during the initiation of antihypertensive treatment. The buffering function of the large arteries has been discussed. Antihypertensive drugs, because of their direct action on the blood vessel wall through the influence on local vasoactive substances or on their receptors, may modify arterial compliance differentially. Recent investigations have shown that some β-adrenergic antagonist blockers and hydralazine-like compounds do not modify arterial compliance despite inducing a reduction in blood pressure. Short- and long-term administration of captopril and enalapril to patients with essential hypertension produce an increase in arterial compliance both in the systemic and brachial circulations. There are several possible mechanisms for this increased arterial compliance. First, the blockade of local angiotensin antagonizes its direct effect on the smooth muscle cell as well as its indirect effect via norepinephrine release. Second, the reduction in blood pressure itself may favor the enhancement of compliance. Third, since the circumferential elasticity of a blood vessel is related to its radius rather than to the pressure itself, the increase in arterial diameter per se caused by converting-enzyme inhibition may play a role. 

Safar et al. examined this possibility by comparing the effects of captopril and isosorbide dinitrate on mean arterial pressure and arterial compliance in patients with hypertension. Both agents reduced blood pressure and increased arterial compliance. Captopril induced an increase in compliance before an increase in distensibility. On the other hand, isosorbide dinitrate increased compliance by increasing arterial volume while having no influence on distensibility. Thus, converting-enzyme inhibitor caused a significant relaxing effect on the wall of the hypertensive artery. This is probably the
result of the blockade of local angiotensin production in arterial smooth muscle rather than the result of a reduction in the dynamic characteristics of the muscle load associated with stretch, since the usual negative correlation observed between pressure and distensibility disappeared after converting-enzyme inhibition. Thus, converting-enzyme inhibition augments the buffering function of large arteries. This unique effect may be important in reducing vascular injury, which may initiate the atherosclerotic processes.

Let us now examine the influence of antihypertensive treatment on afterload and cardiac hypertrophy. It has been suggested that antiadrenergic agents such as methyldopa or propranolol facilitate regression of cardiac hypertrophy, whereas nonspecific vasodilators such as hydralazine do not. Secondary activation of the sympathetic nervous system has been suggested to explain the lack of effect of hydralazine. In a recent study, captopril and cadralazine were studied in patients with essential hypertension. Captopril did not modify arterial distensibility despite a reduction in blood pressure. This was probably due to reflex activation of the sympathetic nervous system. In contrast, captopril markedly increased volume distensibility at the same level of blood pressure reduction obtained with cadralazine. Furthermore, while systolic pressure decreased to a similar extent after the two drugs, heart rate increased significantly only with cadralazine. Therefore, it can be concluded that systolic pressure–heart rate product increases with cadralazine and decreases with captopril. This reduction in systolic pressure–heart rate product with captopril suggests a less pronounced end-systolic stress per unit time after converting-enzyme inhibition.

The effect of vasodilator agents on end-systolic wall stress is extremely important in severe congestive heart failure. Converting-enzyme inhibitors reduce arterial impedance and have been shown to be efficacious in the treatment of dilated congestive cardiomyopathy. Recently, therapy with converting-enzyme inhibitors has been shown to improve the survival of patients with congestive heart failure. Monotherapy with hydralazine has been proven to be of limited value. On the other hand, the recent results of the Veterans Administration heart failure study showed that hydralazine in combination with isosorbide dinitrate was effective in improving subjective and objective performance as well as the survival of patients with heart failure. Since nitrates increase arterial compliance by increasing arterial volume, it is likely that the addition of nitrates to hydralazine is the crucial factor responsible for the efficacy of this combination therapy.

In summary, large arteries play an important role in cardiovascular hemostasis through their conduit and buffering functions. These properties are influenced by various circulating and local vasoactive substances. The vascular renin-angiotensin system is emerging as an important autocrine or paracrine system that influences large and small vessel functions. In hypertensive subjects, there is experimental and clinical evidence to suggest that the reduced arterial compliance may, in part, be due to activation of the local renin-angiotensin system. Indeed, converting-enzyme inhibitors increase arterial caliber and distensibility, which may be important in promoting regression of cardiac hypertrophy, reducing hypertensive vascular injury, and preventing congestive heart failure.

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