Angiotensin II, mechanotransduction, and pulsatile arterial hemodynamics in hypertension

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Lacolley P, Safar ME, Regnault V, Frohlich ED. Angiotensin II, mechanotransduction, and pulsatile arterial hemodynamics in hypertension. Am J Physiol Heart Circ Physiol 297: H1567–H1575, 2009. First published September 4, 2009; doi:10.1152/ajpheart.00622.2009.—The aortic blood pressure curve involves two components: a steady component, the mean arterial pressure (MAP), which is dependent on cardiac output and vascular resistance, and a pulsatile component pulse pressure (PP), which is dependent on arterial stiffness and pulse wave reflections. The transduction mechanisms of MAP and PP differ markedly, involving focal adhesion kinase for MAP and oxygen free radicals for PP. Angiotensin II (ANG II) and its blockade are associated with changed vascular resistance and MAP; however, their effects on PP (peripheral and mostly central PP) have been inadequately investigated. In hypertensive rats, when compared with their normotensive controls, ANG II blockade normalizes central PP (<50 mmHg) but not MAP when the same drug dosage is used for each. In hypertensive patients, ANG II blockade reduces arterial stiffness and pulse wave reflections, but with the same reduction in MAP, there is a greater reduction in central than peripheral PP, thereby increasing carotid-brachial PP amplification. With long-term ANG II blockade, the hypertensive arteriolar hypertrophy observed at baseline is corrected in association with reduced arteriolar reflection coefficients, reduced carotid arterial attachments linking α5-integrin to its ligand fibronectin, and decreased circulating C-reactive protein. When given a normal salt diet, each of these factors contributes separately in reducing arterial stiffness and wave reflections. These responses disappear with a high-salt diet, a condition that usually involves the activation of the local vascular renin-angiotensin-aldosterone system and can be prevented by its selective blockade. Thus ANG II inhibition seems to contribute independently in reducing central PP and aortic stiffness.

antihypertensive therapy; pulsatile forces

...the interaction between the different components of the renin-angiotensin-aldosterone system (RAAS) determines its activity and, in turn, influences the regulation of arterial blood pressure (BP), renal sodium handling, and cardiovascular (CV) risk. Several years ago, the RAAS description was limited to a relatively small number of biochemical factors, including renin, angiotensin (ANG) I and II, aldosterone, and their relevant enzymes, the principal one being the angiotensin-converting enzyme (ACE). From these earlier findings, much fundamental and clinical progress have been achieved, not the least in the prognosis of patients with hypertension and CV diseases, particularly as it relates to treatment. In more recent years, new components, as well as changes in the structures and functions of the RAAS, have been extensively described (53), including renin, prorenin, and angiotensin receptors; a second ACE enzyme, novel biological actions of angiotensin 1–7, ANG II type 2 receptor regulation of renin synthesis, and secretion; and the existence of (e.g., cardiac, vascular, renal, and brain) local RAAS. In the heart, vessels, kidney, and other organs, investigators have shown that novel aspects of pharmacological inhibition of the components and enzymes of the RAAS continue to evolve (53).

Angiotensin inhibition, independent of its effect on mechanical stress, is certainly a major target of prolonged treatment in patients with heart failure and myocardial infarction (37). However, in patients with hypertension, the results of therapeutic trials involving the selective inhibition of angiotensin have not shown that the specific mechanism of action of each agent is responsible independently of mean arterial pressure (MAP) and pulse pressure (PP) for the reduced CV risk. Most important is the residual systolic pressure (SP) resulting from therapy that seems to be one of the major determinants of prognosis (54). In fact, three observations are important when considering the various responses to treatment in hypertensive subjects. First, each of the therapeutic trials have suggested that drug treatment produced an adequate decrease of diastolic pressure (DP < 90 mmHg) rather than an adequate decrease in SP (<140 mmHg) or PP (PP = SP − DP) (48, 54). Second, in...
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each individual patient, the duration of drug treatment may be 30 years or more, whereas the duration of any therapeutic drug trial approximates about five years. Thus it follows that the specific effects of aging per se and the duration of treatment could importantly affect the long-term changes, particularly with respect to the SP level. The brachial SP and, particularly, the nocturnal SP seem to be one of the major intermediate criteria that can determine the effectiveness of treatment (2, 54). Finally, several reports (summarized in Ref. 2) have clearly suggested that central BP measurements (aortic or carotid BP) are a more adequate predictor of CV outcomes than brachial BP in hypertensive patients receiving prolonged treatment.

The purpose of this review is to discuss the respective role of the RAAS, its blockade, and pretreatment BP level in the mechanisms of antihypertensive drug treatment of hypertensive patients. More specifically, the MAP and PP will be considered individually, taking into account the specific arterial site of their measurements, the consistent differences in the hemodynamic mechanisms of MAP and PP, and their respective mechanotransduction. Moreover the impact on the local and systemic RAAS will also be considered (10, 11). Thus this review results from five questions. First, what are the phenotypic aspects of the BP curve? Second, which are the main vascular consequences of long-term angiotensin blockade? Third and fourth, how does the transduction of pressure within the arterial wall differ between MAP and PP during long-term angiotensin blockade? Finally, what are the possible links between the local RAAS within the arterial wall and central PP and wave reflections?

Phenotypes of the BP Curve: Basic Concepts

Large arteries provide two distinct mechanical functions (35, 48, 50). First, there is the conduit function, which is dependent on a slight (but important) mean pressure gradient between the aorta and the smaller resistance arteries and accounts for the forward flow of blood to the peripheral tissues and organs. Second, there is a cushioning function, which dampsen the pressure oscillations resulting from intermittent ventricular ejection (windkessel effect). Although each of the arteries of the vascular tree participate in these two functions, the proximal or more central larger arteries (i.e., aorta and its main branches) have a dominant role in cushioning, whereas the smaller distal arteries and arterioles contribute more to the distribution of blood flow and the determination of vascular resistance. Until recently, studies of the hemodynamic effect of ANG II blockade in humans have been largely restricted to the conduit function (i.e., changes in MAP and vascular resistance) and few efforts have been made to determine which changes in the windkessel function and PP might occur with prolonged treatment with respect to the structure and function of these vessels.

Because of the intermittency of ventricular ejection, the thoracic aorta during systole serves as an elastic reservoir. Thus the amount of blood stored within the arterial wall during systole is forced into the peripheral vessels during diastole, thereby providing a continuous steady flow to be obtained at the capillary level (windkessel effect). For this purpose, the acute pressure pulse generated by ventricular contraction travels along the aorta as a wave. The velocity of this wave, i.e., pulse wave velocity (PWV), represents the traditional surrogate of arterial stiffness measurements: the higher the PWV, the greater the arterial stiffness. Moreover, whereas the SP actually increases with distance from the heart, the MAP falls slightly (about 4 mmHg) during the same course along the aortic length. Consequently, the amplitude of the pressure oscillation between systole and diastole (i.e., the PP) increases significantly. This SP and PP amplification along the arterial tree is a major physiological finding and may approximate 14 mmHg between the origin of the thoracic aorta and the brachial artery, and it is also demonstrated as far distally as the third generation branches of the aorta. This SP and PP amplification tends to disappear with age, but at any given age, it is increased in the presence of tachycardia and decreased with heart rate reduction, a modification frequently produced by β-adrenergic receptor blockade (15, 27, 63). In contrast, ANG II blockade or calcium channel blockade or their combination reduce more central than brachial arterial BP, whereby contributing to maintain, and even enhance, SP and PP amplification and to favor cardiac protection. In contrast, this finding has been poorly observed with the β-blocking agents propranolol and atenolol, which are unable to reduce central (carotid or aortic) PP (27, 63).

Amplification of SP and PP is the consequence of reflected waves that summate with the incident waves at each point along the arterial tree (35, 50). During the propagation of the arterial pressure wave following ventricular ejection, the reflected waves are initiated by any discontinuity of the arterial or arteriolar wall, mainly from the high-resistance arteries and arterioles and from their multiple bifurcations (35, 50). A mismatch in vascular impedance occurs at the junction of high-conductive artery and high-resistance arterioles. Thus the forward pressure wave cannot enter the arterioles and is repelled travelling backward toward the heart. Finally, the morphology of any pulse wave along the arterial tree results from the summation of the incident (forward traveling) and the reflected (backward traveling) pressure wave. Importantly, this summation is considerably influenced by age, so that two different phenotypes of the BP curve may be described clinically and experimentally (35, 50) as follows.

In young adults having achieved full height and maximum elasticity of their central arteries (low PWV), the summation of the incident and reflected waves results in progressive amplification. As a result, the SP and PP are measured higher at the brachial artery than at the thoracic aorta. This hemodynamic profile contrasts with MAP and DP, which fall minimally with distance from the heart in conduit vessels at all ages but not at locations distal to the arterioles. At the level of the thoracic aorta where the PWV is relatively low, the reflected wave returns during diastole, maintaining MAP and DP and enhancing coronary perfusion. Thus an optimal arterial function and adequate coronary perfusion are both achieved.

With age, 50 to 60 yr in humans, the development of increasing arterial stiffness (high PWV) tends to abolish the differences between central and peripheral PP, thereby imparting major consequences on ventricular load as well as on coronary perfusion. Because of the backward pressure, which returns in systole (and not in diastole) as a consequence of enhanced PWV, DP and coronary perfusion tend to decrease, a situation that favors myocardial ischemia. On the other hand, the increased PWV causes the reflected waves to return to the
aortic root earlier during late systole. Under that latter circumstance, the reflected waves summate with the forward-traveling wave, creating an increase or augmentation of the central (carotid or aortic) SP (termed the “augmentation index”) and ventricular load. In elderly persons with isolated systolic hypertension, the aortic SP may be increased by a much as 30 to 40 mmHg (increased augmentation index) as a result of an early return and/or an increased amplitude of wave reflections. This situation favors an increased left ventricular afterload, left ventricular hypertrophy, congestive heart failure, and consequently a greater contribution of PP than MAP.

However, disturbed pulse wave reflections during systole may be functionally reversed under at least three different circumstances. First, angiotensin blockade [due to ACE inhibition, ANG II type 1 (AT1) receptor, or renin blockade] attenuates the amplitude and/or timing of reflected waves either acutely (15, 56) or in long-term treatments (27, 63), thereby resulting in the attenuation of wave reflections and increased SP and PP amplification. Second, acute or chronic insulin administration (using the glucose clamp technique) promotes a similar attenuation of wave reflections (62). This effect disappears in subjects with diabetes mellitus type 1 or with insulin resistance (62). Third, tachycardia, which results in a reduced left ventricular ejection time, causes a shift of the reflected wave from systole to diastole (35, 50, 55). Finally, in the past, angiotensin blockade was studied exclusively in the time domain. Only arteriolar vasodilatation and MAP reduction had been considered hemodynamically. More recently, the effects of angiotensin blockade on the vasculature have been studied on the basis of changes in arterial stiffness and wave reflections, i.e., in the frequency domain. Structural modifications of the vessels, which occur only after prolonged angiotensin blockade, are now also taken into consideration, enabling us to clarify our understanding of MAP and PP during hypertension and its treatment.

Long-Term Angiotensin Blockade and its Vascular Consequences

Structural vascular changes with drug treatment. Most hypertension in patients can be expressed hemodynamically by two different means (50). First, there may be a SP-DP elevation that usually occurs in middle age and is associated with an increased total peripheral resistance produced by arteries with a lumen diameter of <400 μm when relaxed. Wave reflections are minimally developed and contribute to a largely attenuated CV damage. Second, isolated systolic hypertension chiefly occurs in patients over 50 yr of age and is manifested by increased arterial stiffness and disturbed wave reflections that are largely transmitted from small arteries but affect mainly the larger central arteries, thereby favoring major CV damage. These two forms of expression of the hypertensive disease exhibit structural alterations of both the small and large arteries. In the larger (mainly elastic) vessels, the wall thickness increases independently and progressively with age: drug treatment in these patients is mainly able to attenuate this age-related increase in wall thickness (65). In the smaller resistance arterioles, angiotensin blockade (either by ACE inhibition or AT1 receptor blockade) may completely reverse and normalize the structural arteriolar changes of these treated hypertensive patients (47). The same effect is obtained with calcium antagonists but not (or poorly) with β-blocking agents or diuretics alone despite the same degree of brachial BP reduction (52).

Reversibility of structural arteriolar changes with angiotensin blockade has been studied in patients having gluteal muscle biopsies. The structural parameter that has been measured most widely has been the wall thickness-to-lumen ratio of a cylindrical vessel. This alteration has been shown to be an independent predictor of CV events (47, 52). This wall thickness-to-lumen ratio was increased before drug treatment and reduced significantly with angiotensin blockade, ultimately achieving normal values approximately 1 yr after the initiation of drug treatment (47, 52). Significant changes in wall thickness, but not necessarily in lumen diameter, have also been determined. These findings have been frequently termed as arteriolar “remodeling” and have been considered to be associated with parallel changes in vascular resistance and MAP.

Arteriolar bifurcations and wave reflections. To compare gluteal biopsies among histomorphometric studies, it is difficult or even impossible to investigate in vitro arterioles of the same branching order (47, 52). Thus, during angiotensin blockade, a wire myograph method has been considered the most useful to investigate its effects. Thus the role of the branching system itself has been poorly studied histopathologically. Branching points need precise descriptions because they may originate from two or several daughter arteries of different size and stiffness, thus relating to the distribution of different fractions of hematocrit (i.e., viscosity and shear stress) and, hence, blood flow (39). Furthermore, the bifurcation system may suggest quite different sites for the study of wave reflections because of functional or, more likely, structural changes of the vessels. In this context, angiotensin blockade may affect the reflectance properties of the arteriolar system and PP independently of MAP through several arteriolar mechanisms. First, following angiotensin blockade, the resulting changes in the structure of arteriolar branching may itself modify the reflection coefficients pertaining to the pulse wave (Table 1) and, hence, produce reductions in SP and PP (27, 50). Second, the recruitment of immune cells and/or inflammatory factors (e.g., leukocytes) during oxidative stress frequently occurs in the microvascular network (35, 36, 39, 50) and may be associated with changes in amplitude or the timing of wave reflections and result in modifications of SP and PP (1, 27, 48, 55, 56, 63). Age, diabetes mellitus, dyslipidemia, smoking, and other CV risk factors may also contribute importantly to endothelial dysfunction and a disturbed balance between nitric oxide (NO) and oxygen free radicals, which is highly influenced by angiotensin stimulation and blockade (12, 50). Endothelial dysfunction in hypertension is not uniform in the microvessels and may have important consequences on arteriolar branching and, consequently, on the dispersion of reflection sites at the origin of microvasculature (35, 39, 50). Finally, each of these processes tends to favor capillary rarefaction, to extend the reflectant properties of the vascular system, and thereby to produce changes in SP and PP levels independent of MAP, as demonstrated clinically from angiotensin blockade (Table 1).

Role of sodium excess and oxidative stress. In this context, several other factors including sodium intake and oxidative stress may contribute to modify structural vascular changes. Traditionally, the degree of salt and water depletion during angiotensin blockade is known to induce powerful neurohu-
moral mechanisms involving the RAAS and the autonomic system. Such changes are classically explained by secondarily induced arteriolar diameter reduction. In fact, sodium might act through several other pressure-independent pathways affecting the several components of the vascular tree, such as impairment of flow dilatation mechanisms or myogenic tone (29). In addition, sodium binding to glycosaminoglycans located in the interstitial space may be involved with specific consequences on vessel stiffness (7). Finally, sodium excess is associated with reduced capillary density in the microcirculation, particularly in the heart and kidney (9, 13). Each of these responses may develop (in varying degrees) in each vascular territory in association with the suppression of the local renin-angiotensin system and/or decreased NO bioavailability.

With respect to oxidative stress, during a prolonged chronic high-sodium diet, the development of endothelial dysfunction may be stimulated by ANG II and theoretically prevented by ANG II suppression. This may occur even with only a minor change in MAP. However, such studies were minimally involved with specific determinations of local arterial or arteriolar diameter and/or distensibility. Furthermore, other circumstances may be described: ANG II suppression with a high-sodium diet may also be associated with increased oxidative stress and endothelial dysfunction (26, 67), which may be prevented by a subpressor infusion of ANG II (67). The responses of the AT, receptor-induced vasodilatation has been shown to be affected by a high-sodium diet (61) or by hypoxic conditions (38). Furthermore, under ischemic episodes, a certain level of oxygen radicals has been shown to be necessary to obtain an adequate development of coronary collateral growth. Thus normal levels of ANG II are important to maintain vascular function, which may be sensitive to angiotensin blockade (46). Finally, one of the most important questions in this review is to try to reconcile the beneficial effect of treatments targeting the RAAS in hypertension since growing evidence indicates that physiological levels of ANG II suppression by a high-salt diet may promote increased oxidative stress and vascular dysfunction, in addition to a number of other factors (including local RAAS).

For an understanding of this problem, we suggest that under oxidative stress, the role of mechanical stress requires further investigations. Large arteries are continuously exposed to a basal stretch by MAP, which is influenced by the pulsatile component (PP) occurring during each cardiac cycle. This simple observation suggests that vascular smooth muscle (VSM) cells are able to distinguish between pulsatility and steady stretch and, therefore, between those messages associated with MAP and/or PP (24). Current thinking suggests that oxygen free radicals interact mainly with pulsatile stress and that steady pressure may directly interfere with the system of focal adhesion kinase (FAK) (16, 23, 24). In this review we propose that angiotensin stimulation and blockade may act differently on the mechanotransduction of MAP and PP through these different and independent pathways (vide infra).

Transduction of the Vessel Wall, PP, and ANG II

For a long time, the production of oxygen free radicals has been said to occur in endothelial cells exposed to a cyclic stretch of 10–12% (23–25). Thus a 10% cyclic stretch of human coronary artery VSM cells stimulates superoxide anion (O$_2^-$) production, whereas a stretch of 6% had no effect (16, 23).

A significant source of vascular oxygen free radicals has been reported to be generated from membrane oxidase NADH/ NADPH activity, which is controlled by hormones, growth factors, and mechanical forces (25). The basic end product of this enzymatic system is the O$_2^-$, which may be transformed...
quickly into $\text{H}_2\text{O}_2$ by superoxide dismutase. Catalase and glutathione peroxidase then exert a central role in the intracellular detoxification of $\text{H}_2\text{O}_2$ (23, 25). Interestingly, NADH oxidase activity was upregulated in endothelial cells exposed to an oscillatory shear for 24 h, whereas a steady laminar shear induced a more transient response. In fact, by 24 h, steady shear induced superoxide dismutase, unlike oscillatory shear, and this event was consistent even with the atheroprotective quality of laminar flow (25).

Different pathways appear to be involved in mechanical reactive oxygen species (ROS) production in cultured endothelial cells and whole arteries. In endothelial cells, the oxidative response to stretch was found to depend on the bone morphogenetic protein and protein kinase C (PKC). In whole arteries, PKC is rather involved in the oxidative response to steady high-intraluminal pressure but not in response to cyclic stretch. The matrix protein environment could be responsible for the disparity in PKC sensitivity of ROS production between cultured cells and whole vessels exposed to cyclic stretch.

Finally, in vivo studies have shown that pulsatile mechanical signals were able to produce a chronic release of ROS together with flow-induced enlargement and vascular remodeling (6). Taken together, these findings suggest that oxygen free radicals (and their potential equilibrium with NO bioavailability) are major mediators of pulsatile stress. This pulsatility has been considered to be a physiological stimulus that maintains a certain degree of ERK1/2 activation via ROS production (23).

In conclusion, when we consider the differences between MAP and PP and the responses of PP reduction under angiotensin blockade, it seems relevant that free radicals act preferentially on central than on peripheral PP and may exhibit different hemodynamic patterns depending on the vascular territory involved.

### Table 2. Effect of valsartan on body weight, blood pressure, and carotid artery parameters in SHRs receiving a NSD or a HSD

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Valsartan</th>
<th>Placebo</th>
<th>Valsartan</th>
<th>$P$ Interaction (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>14</td>
<td>15</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Body weight, g</strong></td>
<td>412±8</td>
<td>389±10</td>
<td>382±8</td>
<td>378±11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>182±6</td>
<td>144±3*</td>
<td>214±6</td>
<td>180±5*</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PP, mmHg</strong></td>
<td>60±3</td>
<td>42±3*</td>
<td>69±2</td>
<td>69±3</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td>349±11</td>
<td>336±10</td>
<td>347±12</td>
<td>363±11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Distensibility, mmHg$^{-1}\cdot10^{-3}$</strong></td>
<td>2.01±0.16</td>
<td>4.43±0.40*</td>
<td>1.37±0.11</td>
<td>1.61±0.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>$E_{inc}$, kPa</strong></td>
<td>1176±121</td>
<td>539±53*</td>
<td>1659±137</td>
<td>1679±279</td>
<td>0.07</td>
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<tr>
<td><strong>Wall stress, kPa</strong></td>
<td>210±9</td>
<td>168±9*</td>
<td>242±11</td>
<td>198±12*</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n$, number of rats. Note that under normal sodium diet (NSD), valsartan normalizes pulse pressure (PP), not mean arterial pressure (MAP). Under high-salt diet (HSD), valsartan reduces MAP and does not modify PP. SHR, spontaneously hypertensive rat; $E_{inc}$, incremental elastic modulus.

* $P < 0.05$ vs. placebo for the same salt diet; $P < 0.05$, HSD vs. NSD for the same treatment.
on arterial diameter during flow-induced vasodilatation. Since the degree of tangential stresses due to blood viscosity is much less than that of circumferential stress, it seems that arterial stiffness depends mainly on the structure of the media and less on the endothelium that serves mainly as a flow sensor.

Dense plaques, which are composed of cytoskeletal proteins linked to extracellular matrix (ECM) by integrin receptors, are major sites of anchorage between VSM and the ECM and represent key elements for the distribution between mechanical and elastic materials. Integrins exist as αβ pairings and interact with ECM components including fibronectin (Fn; ligand for α5β1 and α5β3), vitronectin (ligand for αvβ3), and laminin (ligand for αvβ1) (32). The interactions of specific ECM proteins with their integrin receptors play a central role in transmitting mechanical forces to VSM (17, 64). Among these integrins present in these dense plaques, a large number are capable of forming complexes with Fn, a glycoprotein that plays an important role in the organization and assembly of the ECM.

When cyclic mechanical strain is applied to matrices containing different adhesion proteins, Fn produces one of the largest mitogenic responses in rat VSM (64). In addition, the expressions of Fn and its α5β1-receptor are increased in spontaneously hypertensive rat (SHR) aorta. The increase of Fn may reflect an increased number of mechanical attachments between the ECM and collagen fibers within the media (5). From a mechanical point of view, an increased number of cell matrix attachments promote increased stiffness and mechanical strength. In addition, Fn is associated with a less-differentiated VSM phenotype and other markers of dedifferentiation such as nonmuscle myosin heavy chain (51). This Fn accumulation promotes an increased capacity of VSM to synthesize the ECM proteins.

These changes have been studied primarily in situations involving normal or increased sodium intake in the presence of ANG II stimulation and blockade (20–22, 28). ANG II and sodium intake represent the major determinants of the elevated Fn in vitro models. Indeed, in SHRs receiving a normal sodium intake, ACE inhibition or AT1 receptor blockade reduced carotid MAP, PP, aortic collagen content, aortic Fn, and α5β1-integrin, leading to a reduction of attachment molecules of Fn and α5β1-integrin as well as an increased isobaric arterial distensibility (20, 21) (Table 2). However, when the SHRs were given a high-sodium diet, the carotid PP and isobaric distensibility remained unchanged with AT1 blockade although the MAP is reduced (Table 2). Contemporaneously, aortic Fn and the attachment molecules remained enhanced (21) (Table 2). Similar observations have been made in Sprague-Dawley rats during chronic aldosterone infusion and a high-sodium diet (22). In this latter study, increased Fn and arterial stiffness as well as aldosterone-induced proinflammatory factors were completely reversed by the selective aldosterone antagonist eplerenone (22). Finally, with the normal sodium diet, RAAS blockade reduced MAP and PP and decreased collagen accumulation, Fn, and its integrin receptor. On a high-sodium diet, MAP but not central PP was reduced in association with collagen accumulation, increased Fn, and increased arterial stiffness.

In respect to the other integrins in the arterial wall, Louis et al. (28) have shown in mice that α1β1-integrin (the receptor for collagen and laminin) was necessary for the development of arterial hypertrophy in response to ANG II. The implicated mechanisms suggested a signaling defect in the mitogen-activated protein kinases (p38 MAPKs) and FAK pathways linked to the integrins (28). It has also been proposed that the increased α5β3 observed in the SHR mesenteric artery may, in part, determine its rigidity as a result of cell proliferation and ECM remodeling (19). Taken together, these findings strongly suggest a prominent role of integrin in the mechanotransduction of steady pressure in SHRs after a prolonged administration of ANG II or aldosterone. Although mechanotransduction of MAP and PP markedly differ, they resulted in the same final pathway of MAPK. It has been reported that steady and pulsatile in vitro stresses activate the ERK1/2 pathways, whereas steady stress is a strong activator of FAK, acting through integrin-ECM interactions and Src family kinase induction (23–25, 28). This hypothesis is not as clear with in vivo models of hypertension (23–25, 28) in which the activation of focal adhesion formations may vary because of arterial wall distension by the pulsatile arterial pressure as well as by an increased mean structural tension.

Nevertheless, it is worth noting that the mechanical contribution of MAP and PP may markedly vary according to age or the vascular territory involved (23, 24). Thus the MAP mechanotransduction may predominate in the heart rather than in the brain or kidney since only the former territory involves active periodic autocontractions. Furthermore, with age, the reflection coefficients are located much closer to target organs (i.e., heart, brain, or kidney) (31). This finding suggests that pulsatility and wave reflections may be transmitted to these organs in the presence of a defect in myogenic tone. This defect is commonly observed in subjects with type 2 diabetes mellitus, subjects with uninephrectomy, some obese patients, and older patients with systolic hypertension (8, 14, 29, 35, 48, 50, 60).

Finally, many factors linked to mechanical stress, particularly pulsatility and wave reflections, may locally affect each particular organ, thereby modulating or interacting with local RAAS.

Local RAAS and Wave Reflections: A Hypothesis

In recent years, compelling experimental and clinical evidence has confirmed the existence of local RAAS in heart, kidney, vessels, and other organs (4, 10, 11, 18, 34, 42). Re and colleagues were the first to postulate the presence of “intracrine” systems (40, 41, 43–45), especially with respect to the local RAAS (41, 42). All the components of local RAAS have been found in VSM cells as well as in renal, endothelial, and, most likely, cardiac myocytes. These cell types are able to generate ANG II locally, and various stimuli have produced an increased oxygen-derived free radical production, which induces oxidative stress and CV fibrosis (10, 11). These local RAAS may be adversely involved in CV structure and function (10, 58, 59, 66). The links between local RAAS and vascular remodeling have been highlighted by the review, suggesting that the in vivo gene transfer of the ACE into the injured rat carotid artery results in vascular hypertrophy independent of systemic factors and hemodynamic effects (33). However, this in vivo design does not exclude the possibility that local vascular pulsatility and/or wave reflections may participate importantly in the development of the organ fibrosis.
One major point to consider in this context is that salt loading not only raises BP (MAP and PP) in salt-sensitive individuals (59, 66) but also suppresses renin release and, at the same time, promotes structural (fibrosis) and functional organ damage, which may particularly affect the CV system and the kidney (10, 11). Recent experimental findings have shown that angiotensin blockade with either candesartan or losartan coincident with salt loading failed to reduce BP while markedly reversing the target organ damage (fibrosis) and function in heart, vessels, and kidney (10, 59). Thus salt loading may not only promote renal renin suppression from juxtaglomerular apparatus but also might even increase angiotensin-induced damage induced by the distal tubular local RAAS (10, 11, 18, 34). It therefore seems likely that not only is angiotensin blockade associated with the control of arterial pressure but that it may also act on local RAAS systems to preserve or (impair) target organ structure and function. It is tempting to suggest that this last aspect might also involve wave reflections in addition to the already demonstrated mitogenic and other functions. Indeed, in subjects with a defective renal autoregulation, we have seen that the reflection sites are closer to the organ and may favor PP transmission (8, 31, 60).

From a therapeutic viewpoint, the administration of a thiazide diuretic to rats is associated with impaired renal hemodynamics, as well as renal structure and function when administered chronically alone or with salt loading (59, 66). Moreover, when the same thiazide dosage is administered with agents producing angiotensin blockade, the adverse pathophysiological effects were prevented (66). It seems reasonable to suggest that these changes may also operate through a second RAAS system (11, 18, 34) that may serve to promote (or protect, within inhibition) the fibrosis and other events affecting the glomeruli, arterioles, and interstitium. Similar findings have been obtained at the level of the heart and large arterial vessels (10, 11, 49, 58, 59). On the other hand, at the site of large arteries, a reduction of MAP by angiotensin blockade in the presence of a low- or high-sodium diet occurs without any interaction between these two conditions of treatment (Table 2). Regarding PP, the situation is different since a significant PP reduction is observed under angiotensin blockade with a low- but not high-sodium diet (21). Finally, complex interactions might occur between local PP and local RAAS and become in the future a key subject for a better understanding of CV target-organ damage (11, 50).

Concluding Remarks

The findings presented herein strongly suggest that, with ANG II stimulation or blockade, high intraluminal steady pressure on the one hand and pulsatile pressure on the other hand are transduced differently in the vascular wall (16, 23, 25). Although both stimuli ultimately may activate the ERK1/2 pathway, only in the case of steady-state stretch is FAK implicated as an upstream mediator. Thus steady stretch is a strong activator of FAK, acting through integrin-extracellular matrix interaction and Src family kinase induction. On the other hand, pulsatility seems to have very little or less impact on FAK phosphorylation in the whole vessel (16, 23, 25).

Thus it is important to distinguish between pulsatile and steady stretch in the whole vessel. In the aorta, pulsatility is a physiological stimulus, given the rhythmic changes in pressure within this vessel imposed by the cardiac cycle. Hence, ERK1/2 activity observed in pulsatile segments presumably represents a basic level contributing to the maintenance of vessel structure and function and, potentially, to the development of atherosclerotic plaque formation. In the case when arterial pressure is elevated, several morphological changes take place in the vessel wall, associated with increased thickness and rigidity of the vessel, as it may be especially demonstrated in hypertensive patients. Supplemental activation of ERK1/2 in this context, transmitted through FAK, may tip the balance toward a proliferative/hypertrophic smooth muscle cell phenotype. Thus MAP and PP may have the same final pathway through MAPK.

Finally, there are key differences with angiotensin in the vascular responses to steady and pulsatile mechanical stresses although both responses are associated. These changes clearly involve the pathogenesis of hypertension at its early phase and are vastly and complexly involved later in its pathophysiological changes and with treatment. In addition, this review emphasizes that much more is to be learned by studying the increasing complexity of the RAAS system locally and systematically in the different aspects of disease subjected to increased CV risk. In this context, it is worth noting that both MAP and PP are independently implicated in CV risk. Increased PP particularly influences the occurrence of atherosclerosis and coronary ischemic disease, whereas MAP seems to have a greater effect on the style and prevention of cerebrovascular complications (54). Following this line of thinking, we suggest novel mechanisms and an hypothesis that relates local RAAS, wave reflections, and associated CV risk.

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REFERENCES

Review

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ANGIOTENSIN AND PULSE PRESSURE


