Clinical Applications of Arterial Stiffness: Therapeutics and Pharmacology

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This short review describes the effects of drugs and nonpharmacologic treatments on large artery stiffness in clinical trials. Arterial stiffness is generally accepted as a predictive factor for cardiovascular morbidity and mortality. The drug-induced reduction in arterial stiffness may parallel the reduction in cardiovascular work. This review summarizes the discussion of a task force that worked on the therapeutic aspects during a Consensus Conference on the "Clinical applications of arterial stiffness," held in Paris on June 17, 2000. The effects of drugs on arterial stiffness are detailed in patients with hypertension, heart failure, and other arterial diseases. Other issues are raised, including the reversibility of arterial changes following pharmacologic treatment, and the possibility for nonpharmacologic treatment to be effective on arterial stiffness. Directions for future therapeutic trials are suggested. Am J Hypertens 2002;15:453–458 © 2002 American Journal of Hypertension, Ltd.

This review focuses on the effects of drugs and nonpharmacologic treatments on large artery stiffness in clinical trials. It summarizes the discussion of a task force that worked on the therapeutic aspects during a consensus conference on the "clinical applications of arterial stiffness," held in Paris on June 17, 2000. Articles selected were in the English language and based on randomized, double-blind studies. Methods for assessing arterial stiffness, which have already described extensively in other reviews, are not discussed here.

Effects of Drugs on Arterial Stiffness

The effects of a given drug on arterial compliance are complex and vary with time. The effects of a vasodilator drug on the arterial wall may be direct, occurring via relaxation of smooth muscle predominantly in the arterial media; or they may be indirect, occurring as a consequence of both a decrease in wave reflection, in response to the dilation and increased compliance of small muscular arteries,[1] and a decrease in mean blood pressure (BP) in response to dilation of resistance arterioles. Other indirect effects are structural and are due to the changes in vessel lumen or wall structure under long-term treatment.

Treatment of hypertension and congestive heart failure (CHF) should aim to increase arterial compliance (ie, to reduce arterial stiffness), to lower afterload and pulse pressure, to promote regression of left ventricular and arterial wall hypertrophy, and, in CHF, to increase in cardiac output. Elevation of diastolic pressure would benefit coronary perfusion, which may be particularly relevant in the setting of coronary artery disease.[2]

Hypertension

In patients with essential hypertension, numerous studies have shown a decrease in arterial stiffness with various pharmacologic classes of antihypertensive agents: β-blockers (BB), diuretics (DIU), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor antagonists (ARA), and calcium antagonists (CA), either acutely or during long-term studies.[3–9] Long-term studies (>3 months) are more meaningful because hypertension is a chronic disease and acute effects may not predict chronic efficacy because of counter-regulatory mechanisms. The ongoing compliance substudy of the European Lacidipine Study of Atherosclerosis trial is the first double-blind comparison of two pharmacologic classes (the CA lacidipine and the BB atenolol) over a 4-year period.[10]

Received November 21, 2000. First Decision November 19, 2001. Accepted November 21, 2001.

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Manuscript from Task Force VI on Therapeutic Aspects, part of the Consensus Conference on "Clinical Applications of Arterial Stiffness," held on June 17, 2000 in Paris, and revised according to the comments of the members of the Consensus Conference.

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0895-7061/02/$22.00
PII S0895-7061(01)02329-9

In most pharmacologic studies, the elastic properties of large arteries have been assessed noninvasively. Direct techniques include measurements of carotid-femoral pulse wave velocity (PWV), an index of aortic stiffness,[4,11] or measurements of cross-sectional distensibility and compliance (carotid, femoral, and radial arteries).[8,12,13] Indirect techniques are frequently based on models of local (brachial)[3] or systemic[5,7,14] circulations. Although the respective advantage and limitations of these various methods have already been extensively discussed (see articles by the other groups in the Consensus Conference published in the *American Journal of Hypertension*), direct methods requiring no assumption concerning hemodynamics are preferable in clinical pharmacology.

Carotid-femoral PWV, despite its limitations, is the easiest method to apply to pharmacologic trials and gives information on the elastic properties of the thoracic and abdominal aorta. Carotid-femoral PWV is an independent predictor of cardiovascular mortality[15] and primary coronary events[13] in a general population of hypertensive patients. Pulse wave velocity can be coupled to the determination of cross-sectional distensibility (mathematical dimension equal to the inverse of PWV) at various arterial sites, which requires the measurements of diameter and stroke change in diameter (with high resolution echotracking systems) and pulse pressure. Direct measurement of local pulse pressure with aplanation tonometry is preferable to estimation from brachial pulse pressure, to avoid errors due to pulse wave amplification between central and peripheral arteries.[1,9] Under these conditions, robust determinations of cross-sectional dynamic distensibility can be performed and applied to pharmacologic trials. Because cross-sectional compliance is the mathematical product of cross-sectional distensibility and lumen area, an advantage of this measurement is that information pertaining to drug-related effects on changes in diameter, and thus the respective contributions of diameter enlargement and increased distensibility, may be derived. A further advantage is that it allows the study of regional differences. This is a particularly important aspect of clinical pharmacology, since drug effects may differ for various types of arteries.[9,16–18]

Pharmacologic trials should focus on large proximal elastic arteries (such as the aorta and the common carotid artery) because they represent the largest part of systemic compliance, which has the most impact on left ventricular load. Although muscular arteries, like the brachial, radial, and femoral arteries, contribute only to a small percentage of total compliance, they are of interest to determine the contribution of smooth muscle relaxation to the increase in arterial compliance. Improving compliance of distal muscular arteries can decrease PWV and reduce the contribution of wave reflections to left ventricular afterload.[1] Reducing mechanical stress, either steady or pulsatile, at the site of proximal elastic or distal muscular arteries, is a desirable goal of drug treatment, to reduce arterial wall hypertrophy.[9] Indeed, although arterial wall hypertrophy does not necessarily decrease arterial compliance, as in the case in essential hypertension,[19] it favors the development of atherosclerosis.

The repeatedly demonstrated efficacy of antihypertensive agents to lower arterial stiffness is not surprising, because BP reduction unloads the stiff components of the arterial wall, such as collagen. Whether classes of antihypertensive agents vary in their efficacy to affect arterial structure and thus influence arterial compliance via a pressure-independent mechanism is more controversial and remains to be evaluated in large scale trials or in meta-analysis of smaller studies. Most of the published studies have included small groups of patients (<20 patients/group), and are thus underpowered to conclude a lack of efficacy of one drug versus another. Despite these limitations, it is so far generally accepted that ACEI, CA, and DIU share a similar ability to decrease arterial stiffness in hypertensive patients in long-term studies. It is also well accepted that the nonselective BB propranolol and the selective β_1-blocker atenolol are less efficacious during long-term treatment than are pindolol, dilevalol, celiprolol, and nebivolol (four BB with vasodilating properties).[3,7,9,20,21]

The efficacy of various pharmacologic classes of antihypertensive drugs on arterial stiffness has been compared with a meta-analysis.[22] This study collected individual data from seven randomized, double-blind, parallel-group trials performed under similar methodologic conditions in a total of 185 patients with essential hypertension, and compared the effect of antihypertensive drugs to placebo on carotid-femoral PWV during long-term treatment (4 weeks to 5 months). No significant difference was detected among the pharmacologic classes (ACEI: cilazapril, lisinopril, quinapril, ramipril, trandolapril; BB: bisoprolol; DIU: hydrochlorothiazide, CA: all dihydropyridines [DHP], felodipine, lacidipine, nitrendipine). All improved PWV to the same extent, relative to BP reduction. However, there was a trend for the DHP to have less efficacy than ACEI, BB, or DIU. The well-established activation of the sympathetic nervous system by CA and, particularly, DHP suggests that they may increase compliance to a lesser extent than ACEI and DIU in long-term studies. This should be confirmed by further cumulative meta-analyses.

Drug efficacy with regard to arterial stiffness may also be influenced by genetic background. For instance, patients carrying the C allele of the A1166C polymorphism of the angiotensin II AT_1-receptor improved arterial stiffness to a larger extent after the ACEI perindopril as compared with the CA nitrendipine, and the reverse was observed in patients homozygous for the M allele.[23] Clinical trials should consider including the study of genetic polymorphisms of candidate genes, not only of the renin-angiotensin system but also of the various systems involved in arterial structure, vasomotor tone, and remodeling. Pharmacogenetic studies should be performed according to the state of the art. Although nitrates are not generally used as antihypertensive drugs, their actions as

powerful smooth muscle relaxants in large arteries[24] are known to improve arterial compliance in hypertensive patients after acute administration.[7,16] Furthermore, such actions in the setting of coronary disease, where their use is routine, may facilitate coronary perfusion through effects on diastolic pressure. The new nitric oxide (NO) donor sinitrodil increases arterial compliance in healthy young men in doses that do not affect the resistance vessels.[25] This effect, which raises the possibility of selectively influencing large artery properties by pharmacologic means, requires confirmation in hypertensive patients during long-term treatment. Indeed, the efficacy of the chronic administration of nitrates is limited by the tolerance phenomenon. A preliminary study showing no tolerance of nicorandil and isosorbide dinitrate for the improvement of carotid and femoral distensibility is encouraging.[12]

It seems likely that pharmacologic treatment is able to improve arterial stiffness beyond BP reduction, because long-term drug administration can modify the wall components, including a reduction in collagen density or changes in the spatial arrangement of the wall materials. Such a pressure-independent increase in compliance has not been unequivocally shown during long-term treatment in individual studies in hypertensive patients, particularly at the site of proximal elastic large arteries. A meta-analysis on individual data[22] was required to show that the pressure-independent reduction in aortic stiffness (carotid-femoral PWV) after active treatment (ACEI, BB, DIU, or CCB) was observed only under chronic conditions and not after acute treatment.

A pressure-independent decrease in arterial stiffness implies a pharmacologic remodeling of the arterial wall. Various changes have been described in response to long-term antihypertensive treatment in animals. They include a reduction in collagen content and density, an increase in the elastin/collagen density ratio, a decrease in intima-media thickness, and changes in the connections of smooth muscle cells to extra-cellular matrix through fibronectin-integrin relationships. In clinical trials, the remodeling of large arteries in response to long-term treatment was non-invasively detected with ultrasound and was characterized by a reduction in arterial lumen and intima-media thickness.[8,9] The regression of arterial wall hypertrophy and the reduction in arterial lumen were dependent on the reduction in local pulse pressure rather than on the lowering of mean BP.[9] These findings underline the effects of cyclic stress on arterial remodeling, and the requirement of lowering pulsatile stress through a decrease in arterial stiffness to obtain a significant pharmacologic remodeling of large arteries.

By contrast, at the site of muscular arteries, a pressure-independent decrease in arterial stiffness may be observed after acute administration, thus suggesting an effect of smooth muscle relaxation on elastic and collagen elements.[1]

Most pharmacologic trials have been performed in middle-aged patients with essential systolic-diastolic hypertension. Special populations of hypertensive patients should be more often studied, including elderly patients[8] and patients with end-stage renal disease,[26] both having a predominantly systolic hypertension characterized by a reduced arterial compliance.

Congestive Heart Failure

Nitrates and ACEI are effective in increasing systemic arterial compliance in patients with congestive heart failure (CHF), thus leading to a subsequent increase in stroke volume in parallel with a prominent reduction in left ventricular filling pressure.[27] The increase in radial artery compliance, observed after 8 weeks of oral administration of the ACEI benazepril, could reflect the sustained improvement in systemic hemodynamics,[28] and is consistent with the well established efficacy of ACEI for improving survival in patients with class II to IV CHF. Long-term studies suggest that the favorable acute effect of nitrates is maintained in response to high-dose oral isosorbide dinitrate therapy and that it is associated with relief of symptoms and improved exercise tolerance. Indeed, when combined with hydralazine, isosorbide dinitrate therapy has been shown in the Veterans Administration study to prolong survival in patients with New York Heart Association class II and III CHF.

Other Arterial Diseases

The effects of drugs on arterial stiffness in normotensive patients with cardiovascular risk factors including diabetes, hypercholesterolemia, smoking, and postmenopausal estrogen deficit have been poorly studied. In hypertensive patients with familial hypercholesterolemia, radial artery compliance was increased to a large extent after a 2 year-treatment with simvastatin, whereas no significant change was observed after treatment for 6 months only.[29] Other studies using short-term treatments did not show any significant improvement. This indicates that the time needed to improve arterial stiffness in these patients can be extremely long.

Systemic compliance is higher and aortofemoral PWV and central pulse pressure are lower in women receiving hormonal therapy, suggesting that such therapy may decrease stiffness of the aorta and large arteries in postmenopausal women.[30] Futhermore, removing women from their hormonal therapy for 4 weeks reduced arterial compliance, and then reinstating therapy for another 4 weeks restored compliance to prestudy levels, independently of BP changes.[30] Long-term randomized trials are warranted to further validate this hypothesis and to determine the efficacy of hormonal therapy in the prevention of age-related large artery stiffening.

Reversibility of Arterial Changes Following Pharmacologic Treatment

Optimal pharmacologic treatment would fully normalize arterial stiffness through the combined effects of BP lowering and vascular structural changes. In recent long-term clinical trials, the increase in cross-sectional carotid artery distensibility[8,9,25] and the decrease in PWV did not normalize arterial stiffness.[11,22,31] To reach full normalization of arterial stiffness, pharmacologic and therapeutic trials should do the following: 1) aim at lower systolic and diastolic BPs to a larger extent than in most previous studies; 2) give treatments for a longer duration than in most previous studies[29]; and 3) select patients according to relevant genotypes.[23] However, despite considering duration of therapy, degree of BP normalization, and genotype, arterial stiffening may still prove at least partially irreversible particularly in older individuals due to degradation of the elastic matrix, aortic atherosclerosis, and calcification.

Nonpharmacologic Treatment

The literature examining the efficacy of nonpharmacologic therapies, including exercise training and dietary manipulation to influence arterial properties, is expanding rapidly, although most intervention studies have involved relatively small numbers of subjects. Aerobically trained athletes have greater large arterial compliance than matched sedentary controls.[32] This relationship also appears to hold for normally active elderly individuals, in whom arterial compliance was positively correlated with time to cessation of exercise during a standard Bruce protocol treadmill test.[33] A single 30-min bout of cycling exercise at 65% of maximal oxygen consumption induced a small but significant increase in aortic compliance and a reduction in PWV and central systolic BP[34] by mechanisms that may relate to vasodilation. Furthermore, 4 weeks of moderate intensity exercise (65% maximum) performed for 30 min, three times weekly, in previously sedentary individuals increased resting arterial compliance.[35] Although part of this change was BP dependent, normalization of compliance to a standardized mean arterial pressure suggested modification of intrinsic arterial elastic properties. By contrast, the proximal aorta and the leg arteries are stiffer in strength-trained individuals and contribute to a higher cardiac afterload.[36]

Weight loss in healthy obese men induced a significant fall in mean BP, which was associated with a tendency toward a BP-dependent increase in large artery compliance.[37] Fish oil therapy for 6 weeks improved systemic arterial compliance in non–insulin-dependent diabetes mellitus, whereas no change occurred in BP, cardiac output, or systemic vascular resistance.[38] Furthermore, α-linolenic acid, the plant precursor of fish fatty acids, increased arterial compliance in obese subjects.[39] In a cross-sectional study, low sodium intake was associated with lower PWV in individuals >30 years of age.[40] Pulse wave velocity increased less in healthy adults who were taking >300 mg daily of standardized garlic powder for >2 years than in age- and sex-matched control subjects.[41] Finally, isoflavones derived from either soy products or red clover increased large artery compliance in postmenopausal women.[39]

Therapeutics Development

Among the already existing antihypertensive drugs, there is still a need to better define their effects on large artery properties independently of BP lowering. In view of the important local actions of angiotensin II on arterial stiffening (fibrosis, collagen synthesis),[18] drugs interfering with the renin-angiotensin-aldosterone system (RAAS) are important candidates. Recent data indeed suggest pressure-independent effects of ACE inhibitors.[18,22] Additional potential candidates along the RAAS axis are aldosterone antagonists. Aldosterone is an important mediator of fibrotic changes at the level of the heart and recent data suggest that similar effects may occur in the arterial wall of rats[42] and humans.[43] Studies investigating the effects of spironolactone (and the more selective aldosterone antagonist eplerenone) on arterial stiffness in patients with essential hypertension or primary hyperaldosteronism are clearly warranted.

The second potential group of drugs to further develop is that of nitrates/NO donors. As discussed earlier here, there is now clear evidence that within a certain dose range this class of drugs can act relatively selectively on large arteries. This implies that they may potentially interfere with arterial stiffness without a strong effect on peripheral resistance. The newly developed dual inhibitors of NEP (neutral endopeptidase) and ACE are interesting molecules in that they share the smooth muscle–relaxing effect of nitrates, through the increase in intracellular cGMP and the inhibition of the effects of angiotensin II on the vessel wall.[44] As yet there are no published data examining their action on arterial stiffness.

A third approach is to circumvent hemodynamic effects and to directly target the molecular events leading to arterial stiffening. A potential molecular target in this respect is the formation of advanced glycation end-products (AGE). These products are responsible for the arterial stiffening in conditions such as diabetes[45] and aging[46] in animal models. Drugs interfering with the formation of AGE, such as aminoguanidine and ALT-711, have been shown in animal models to reverse arterial stiffening without influencing BP.[46,47] In particular, ALL-711 is able to improve total arterial compliance in aged individuals with vascular stiffening.[48] These data require clinical follow-up in pathophysiology (eg, diabetes and isolated systolic hypertension) and pharmacology.

A more futuristic approach is the pharmacologic interference with collagen metabolism. This is a particularly difficult target in view of the extremely low turnover of

this vessel wall component. Early attempts in experimental models of hypertension[49] were promising, but have not been developed in the clinical setting.

Future Therapeutic Trials

In addition to the potential novel pharmacologic avenues described above, new therapeutic trials are needed to better define the potential profit of influencing arterial stiffening. One aspect to be dealt with is that of pharmacogenetics. It would be useful to determine whether a specific genetic make-up (in particular, in terms of gene polymorphisms) could contribute to a better profiling of drug sensitivity.[23] Such studies will probably require large-scale population approaches, but are worthwhile undertakings in view of their potentially broad implications in rational therapeutic decision making.

A second urgently needed type of clinical trial should define, in terms of outcome (ie, morbidity and mortality), whether reduction in arterial stiffness is a desirable therapeutic goal. Again, this would involve a large-scale population study. On the other hand, large artery properties may provide useful intermediate end points to assess therapeutic interventions, which correlate more closely with the initial cardiovascular risks compared to mortality and morbidity end points.

Finally, a special focus of attention of future clinical trials should be on systolic hypertension and the role of pulse pressure in overall cardiovascular risk. Other sections of this Consensus Meeting will deal with that matter in much more detail.

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