Studies on Arterial Stiffness and Wave Reflections in Hypertension

Michel E. Safar and Bernard I. Levy

BACKGROUND
Pathophysiological and pharmacological studies have consistently noticed that, with the exception of subjects with end-stage renal disease, total intravascular blood volume is not increased in patients with chronic hypertension.

METHODS
Because the mean circulatory pressure is enhanced in such subjects, it was postulated that the compliance of the cardiovascular system could be abnormally low in this particular population. This simple observation has influenced a great part of our experimental and clinical research directed toward subjects with hypertension and their relationship with the compliance of the vascular system.

RESULTS
These works started between 1970 and 1980 by methodological investigations and validations followed by analysis of clinical situations that showed that venous and mostly arterial stiffness were significantly increased in hypertensive patients independently of blood pressure level. During the same time, we assessed the role of endothelium on the large arterial wall mechanical properties in normotensive and hypertensive rats. Thereafter more specific directions have been developed, affecting large arteries structure and function and arterial wall remodeling, including their consequences on central and peripheral hemodynamics. In parallel, epidemiological studies identified the pulsatile hemodynamic parameters as major independent predictors of cardiovascular risks.

CONCLUSIONS
The consequences of these alterations on clinical pharmacology and therapeutics in hypertension are analyzed in detail.

Keywords: arterial stiffness; blood pressure; hypertension; wave reflections.

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Studies devoted to drug treatment of arterial hypertension have consistently involved nephrology, hemodialysis, and transplantation, all subjects leading to investigations on sodium balance, fluid volumes, and kidney functions. Authors of those studies primarily observed that, with the exception of end-stage renal disease (ESRD) patients, total intravascular blood volume is not increased in chronically hypertensive patients. However, because their mean circulatory pressure is enhanced, it could be postulated that cardiovascular (CV) system compliance might be abnormally low in this particular population. That simple hypothesis has oriented much clinical research on subjects with hypertension to explore the characteristics of vascular system elasticity. Those studies started between 1970 and 1980 with methodologic investigations and analysis of clinical situations. Thereafter, examination of more specific targets was undertaken, affecting mainly histomorphometry, vascular remodeling, epidemiology, clinical pharmacology, and therapeutic approaches.

METHODOLOGIC BASIS

From 1970 to 1980, 2 important questions were addressed. The first concerned the conceptual basis of clinical investigations on hypertensive subjects compared with normotensive control subjects: Is cardiac output normal in essential hypertension? The second addressed the choice of devices enabling adequate investigation of arterial system elasticity in clinical settings.

To evaluate cardiac output in hypertensive subjects by comparison with normotensive control subjects, the principal problem was to reconcile the invasive measurements of cardiac hemodynamic parameters with the use of the Guyton model, which is the most widely used model to describe the human CV system. In this context, the Guyton model was limited to the classical negative feedback loop characterizing the control of cardiac output, fluid volumes, and the kidney in subjects with normal blood pressure (BP) or hypertension. Investigations proceeded in successive steps, as follows.

First, using hemodynamic measurements from approximately 1,000 subjects, 3 clinical protocols were successively established to determine baseline measurements and statistical cross-sectional analyses; the effects of acute and rapid blood-volume expansion under iso-osmotic dextran infusion into hypertensive patients; and repeated hemodynamic investigations with long-term follow-up of a large population of borderline hypertensive subjects.

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Second, several Guyton model equations were adapted using original procedures, enabling exclusive consideration of steady-state measurements. The latter were sequentially evaluated in the normotensive and hypertensive subject populations and then compared.

Third, it was shown that, to obtain the same cardiac output level in normotensive and hypertensive subjects, several Guyton model coefficients had to be modified, particularly coefficients related to the structural changes of the vessels and the reduction of arterial and venous vessel elasticity parameters. Furthermore, the vascular properties observed in hypertensive subjects were shown to have significant consequences on the degree of cardiac hypertrophy, the distribution of fluid volumes, and, finally, the level of renal function. All of this original research was published by our group in section IV (volume 1) of Laragh and Brenner’s book on the mechanisms of hypertension.

The results of all of those early studies clearly showed that the parameters characterizing the vascular system were lower in hypertensive arteries and veins, when assessed according to the Guyton model. Our research then focused mainly on “large arteries in hypertension” for several reasons. First, systolic hypertension was responsible for the majority of cardiovascular (CV) events, particularly in the elderly. At that time, therapeutic trials in this field were just emerging. Second, antihypertensive drug treatment was associated with dramatically fewer CV events through normalization of diastolic BP (DBP; ≤90 mm Hg); however, at that time, systolic BP (SBP) was still poorly modified by drug therapy. Finally, equations describing the vascular system began to be more extensively analyzed; it then became apparent that it was important to dissociate the role of mean BP from that of pressure pulsatility and vessel characteristics.

Initially, the Windkessel model was the only one used to evaluate the buffering function of large arteries. This procedure was then validated in normotensive and hypertensive subjects. Because the Windkessel model is not a propagative model, Safar, Levy, and Struijker-Boudier, drawing on the initial results obtained by Moens and Korteweg, proposed that pulse wave velocity (PWV) measurements be used instead. PWV was determined between carotid and femoral artery sites. Finally, various local vessel properties and diameter parameters were measured, particularly on the brachial, radial, carotid, and/or femoral artery, and even thoracic aorta sites. In Paris (Broussais Hospital), Pierre Peronneau, an engineer working on velocity procedures, developed a device enabling determination of brachial artery diameter and distensibility. This device was validated and then used for the first time in clinical research. Later, with the help of Struijker-Boudier and Rahn (Maastricht, The Netherlands) and Brunner (Lausanne, Switzerland), Hoeks in Maastricht developed and validated novel devices for carotid and radial artery diameter measurements using echo-tracking procedures. Now, carotid and radial artery wall intima-media thicknesses could be measured in parallel. Most of those measurements were originally developed at Broussais Hospital. Finally, Broussais Hospital became one of the first medical institutions in the world to routinely and noninvasively measure arterial stiffness and its numerous parameters (compliance, distensibility, and incremental elastic modulus) in humans. Those studies were frequently conducted with the help of Michael O’Rourke (Sydney, Australia), particularly the measurement of local pulse pressure (PP) and tonometric evaluation of various parameters involving central wave reflections. Several publications ensued, summarized mainly in Swales’s *Textbook of Hypertension.*

### LARGE ARTERY STRUCTURE AND FUNCTION

Under the direction of B. Levy, normotensive Wistar Kyoto (WKY) rats and spontaneously hypertensive rats (SHRs) were used to establish arterial compliance vs. transmural pressure curves under *in vivo* and *in situ* conditions. At the higher transmural pressure values, corresponding to the presence of predominant collagen-fiber stretch, isobaric compliance was the same in normotensive and hypertensive rats. At operating pressure, isobaric compliance was lower in hypertensive than normotensive rats, even after potassium cyanide poisoning of vascular smooth muscle (Figure 1), thereby highlighting the major role of structural vascular changes in the mechanism of reduced compliance in hypertension.

However, the most original observation concerning arteries was the impact of de-endothelialization. Notably, loss of endothelium led to increases of carotid diameter and distensibility that were less pronounced in hypertensive animals than in normotensive animals. That experiment demonstrated, for the first time, that, in the presence of endothelium, powerful vasoconstrictive mechanisms contribute to maintaining normal carotid vascular properties through their equilibrium with nitric oxide bioactivity.

![Figure 1. Effects of endothelium removal on carotid compliance (cc) in normotensive and hypertensive rats (mean ± SD). WKY E+, Wistar Kyoto normotensive rats with intact endothelium under control conditions; WKY E−, normotensive rats with damaged endothelium; SHR E+, spontaneously hypertensive rats with intact endothelium under control conditions; SHR E−, spontaneously hypertensive rats with damaged endothelium.](image-url)
Thereafter, the mechanical behavior of in situ rat carotid arteries was studied successively under static and dynamic conditions using transmural pressures ranging 50–200 mm Hg. The static pressure–diameter relationship shifted to higher diameter values in the SHRs, compared with WKY rats, mainly because of a larger unstressed carotid diameter in the former. In contrast, carotid compliance and distensibility were similar under dynamic conditions, close to in vivo PP values. Hence, it was concluded that larger lumen carotid arteries in hypertensive rats could compensate for a stiffer arterial wall, resulting in similar dynamic compliance in normotensive and hypertensive rats. Similar results were obtained at carotid and radial artery sites in hypertensive men, together with the presence of vascular hypertrophy and lumen enlargement.

All of those findings were finally corroborated in human and rat models in the presence of a particular and unique CV risk factor: hypertension. Reductions of compliance and/or distensibility independently of BP were also observed in the presence of several other CV risk factors (e.g., aging, obesity, diabetes mellitus, metabolic syndrome, peripheral arterial disease, and, mainly, ESRD). In humans, arterial stiffness seemed to increase significantly with the degree of endothelial dysfunction and, therefore, the number of risk factors involved.

In ESRD patients on chronic hemodialysis, London et al.’s clinical study results showed that BP is mostly represented by systolic hypertension and associated with increased aortic stiffness and disturbed wave reflections. Such changes were independent of mean BP but largely influenced by the presence of arterial calcifications, endothelial dysfunction, and vascular remodeling. Furthermore, in ESRD patients, increased aortic stiffness is a strong independent predictor of all-cause and mainly CV mortality. A therapeutic trial on ESRD patients showed that long-term BP reduction resulting in significantly prolonged CV survival was mainly observed in those patients showing adequate BP and aortic stiffness control, particularly when salt and water were restricted and associated with angiotensin-converting enzyme (ACE) inhibition. In contrast, patients with appropriate BP reduction but constantly elevated aortic stiffness had worse prognoses.

PULSATILE ARTERIAL HEMODYNAMICS AS INDEPENDENT PREDICTORS OF CV RISK

Further studies showed, for the first time, that brachial PP, aortic PWV, and, to an even higher extent, central PP and wave reflections were independent predictors of CV risk, mainly in the elderly.

A French study done in 1989 in normotensive and untreated hypertensive adults was proposed to determine a pulsatile component index. This index was derived by principal components analysis of SBP and DBP measurements and was strongly correlated with brachial PP. An association was found between the pulsatile component index and electrocardiographic evidence of left ventricular hypertrophy. During 10 years of follow-up, the pulsatile component index was independently associated with an increased risk of death from coronary artery disease but not stroke. The relationship was consistent for women aged >55 years, indicating for the first time that PP was an independent CV risk factor.

In another prospective study evaluating hypertensive subjects in New York, Alderman et al. confirmed similar findings in men and women.

Franklin et al., for the Framingham Heart Study; Millar et al., for the Medical Research Council Trial; and Blacher et al. for the EWPHE, Syst-China, and Syst-Eur trials, showed almost simultaneously that, after 50–60 years, brachial PP was a stronger CV risk factor than SBP alone for myocardial infarction in populations of hypertensive individuals. The best predictive function of all possible linear combinations of SBP and DBP was shown to be similar to that of PP, indicating that their association was not a statistical artifact caused by the SBP–PP correlation. Results of a longitudinal study showed that, during 20 years of follow-up, subjects with higher CV mortality were those whose SBP rose and DBP declined, and their CV mortality rate was significantly higher than that for those whose SBP and DBP rose together. Finally, brachial PP was also shown to be an independent predictor of CV risk in ESRD and/or diabetes mellitus patients.

Based on 19,083 normotensive or hypertensive men followed for 20 years, Benetos et al. confirmed not only that elevated brachial PP was a strong predictor of myocardial infarction but also that its predictive value held true even for a normotensive population, especially men aged >55 years, and particularly those taking antihypertensive drug(s).

Epidemiologic studies on ESRD patients identified 3 predictors of CV mortality and overall mortality: aortic PWV, age, and duration on hemodialysis. After adjusting for confounding variables, the odds ratio for PWV (>12 m/s) was 5.6 (95% confidence interval (CI) = 2.3–15.3) for CV mortality. In contrast, identifying predictive factors contributing to essential hypertension is more complex. Indeed, long-term longitudinal studies with aortic PWV measurements are difficult to conduct, mainly because of differences between the sexes and particularly the mobility of young subjects. However, the calculated CV risk obtained with the Framingham equations can partly resolve these difficulties. In a study on 530 hypertensive subjects, the CV risk assessed using the Framingham score was linearly associated with the PWV increase. Furthermore, aortic PWV was shown to be the best predictor of CV mortality. The odds ratio of being at high risk of CV mortality (>5% for 10 years) for patients with PWV >13.5 m/s was 7.1 (95% CI = 4.5–11.3). Results of longitudinal studies confirmed that aortic PWV is a significant and independent predictor of CV risk, better than PP itself.

Finally, aortic PP is expected to be more relevant for the evaluation of CV risk than brachial PP because it is closer to the heart and coronary and carotid arteries, which are the most important sites of CV events. In ESRD patients, aortic PWV, carotid wave reflections, and mostly central PP were shown to independently predict CV mortality (Table 1).
Table 1. Area under the receiver operating characteristic curve, crude and adjusted hazard ratios for all-cause mortality per 1-SD increment of mechanical variables

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Mean ± SD</th>
<th>Area under the ROC curve</th>
<th>HR per 1-SD Increment (95% CI)</th>
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<tr>
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<td>Crude</td>
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<td>Adjusted</td>
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<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>156 ± 28</td>
<td>0.64 ± 0.10</td>
<td>1.3 (1.0–1.7)</td>
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<td>1.1 (0.8–1.3)</td>
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<tr>
<td>Carotid systolic BP, mm Hg</td>
<td>152 ± 29</td>
<td>0.71 ± 0.11</td>
<td>1.6 (1.2–2.1)</td>
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<td>1.2 (0.8–1.4)</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>83 ± 15</td>
<td>0.65 ± 0.10</td>
<td>0.5 (0.4–0.7)</td>
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<td>0.8 (0.6–1.0)</td>
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<tr>
<td>Mean BP, mm Hg</td>
<td>108 ± 17</td>
<td>0.50 ± 0.09</td>
<td>0.8 (0.7–1.1)</td>
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<td>0.7 (0.9–1.2)</td>
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<tr>
<td>Brachial PP, mm Hg</td>
<td>73 ± 23</td>
<td>0.78 ± 0.11</td>
<td>1.8 (1.5–2.3)</td>
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<td>1.2 (0.9–1.5)</td>
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<tr>
<td>Carotid PP, mm Hg</td>
<td>68 ± 25</td>
<td>0.84 ± 0.11</td>
<td>2.2 (1.7–2.7)</td>
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<td>1.4 (1.1–1.8)</td>
</tr>
<tr>
<td>Brachial/carotid PP, %</td>
<td>110 ± 16</td>
<td>0.85 ± 0.11</td>
<td>0.2 (0.1–0.4)</td>
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<td>0.5 (0.3–0.8)</td>
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<tr>
<td>PWV, m/s</td>
<td>11.7 ± 3.1</td>
<td>0.83 ± 0.11</td>
<td>2.1 (1.7–2.6)</td>
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<td>1.3 (1.0–1.7)</td>
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<tr>
<td>LV mass index, g/m²</td>
<td>172 ± 46</td>
<td>0.68 ± 0.11</td>
<td>1.5 (1.2–1.8)</td>
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<td>1.2 (0.9–1.6)</td>
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</table>

Adjustments were made for age at inclusion, time on dialysis before inclusion, and previous cardiovascular events. Hazard ratios (HRs) in bold type differ significantly from 1.

Abbreviations: BP, blood pressure; CI, confidence interval; LV, left ventricular; PP, pulse pressure; PWV, pulse wave velocity; ROC, receiver operating characteristic.

Those findings were confirmed in elderly hypertensive subjects. The validity of central PP as predictor of CV risk is now consensually accepted.

**CLINICAL PHARMACOLOGY AND THERAPEUTICS STUDIES**

Because clinical and epidemiologic studies indicated that large arteries might be a major target for antihypertensive therapy, it was important to show that drug therapy in hypertensive animals could really modify the structure and function of arteries. Although such an effect was easily demonstrated for long-term drug treatment, it was more difficult to determine whether the reversibility of large artery changes was attributable to lowering BP alone, a local impact of each antihypertensive agent on the large artery wall, or a combination of both factors. Therefore, a set of experiments specifically used an ACE inhibitor (ACEI), angiotensin II AT1 receptor blockade, or selective aldosterone antagonists. They showed that (i) regression of aortic hypertrophy was affected by BP reduction alone, whereas diminution of the arterial wall-collagen content was independent of BP lowering; (ii) decreasing collagen content in the aortic wall was caused by blockade of AT1 or mineralocorticoid receptors but not bradykinin; and (iii) AT1 or mineralocorticoid receptor blockade was associated with reduced wall material stiffness, independent of BP and/or wall-stress changes, a finding predominantly observed under a low-sodium diet.

In hypertensive humans, it was important to demonstrate that large arteries were not passive conduits but involved vasoactive responses independently of BP changes. Results of double-blind studies showed that, despite lowering BP, which is able to decrease arterial diameter passively, various antihypertensive agents were able to dilate muscular peripheral arteries, thereby demonstrating their active in vivo relaxing actions. A more difficult issue was to show that antihypertensive drugs were also able to increase compliance and distensibility independent of, and in association with, BP changes. First, we showed that some antihypertensive agents (e.g., propranolol, dihydralazine, and diuretics) were unable to increase compliance and distensibility, despite adequate BP reduction. Second, we clearly demonstrated that, during long-term follow-up, ACEIs increased peripheral muscular arterial compliance and distensibility and/or improved carotid wave reflections independently of BP changes.

That pivotal finding was demonstrated in the REASON study, which was the first to investigate long-term interactions among PP, arterial stiffness, and wave reflections in relationship to drug treatment and end-organ damage (cardiac mass) of hypertensive subjects. Treating them for 1 year with the ACEI perindopril (Per) combined with low-dose indapamide (Ind) was compared with treatment with the beta-blocking agent atenolol. For the same DBP and mean BP reductions, Per–Ind lowered SBP and PP more than atenolol. The reductions were more pronounced centrally (carotid artery) than peripherally (brachial artery). Although the 2-drug regimens lowered PWV equally, only Per–Ind lowered the wave reflection augmentation index. In addition, Per–Ind diminished cardiac hypertrophy more than atenolol, and that decline was attributed to carotid wave reflections, thereby indicating their role in cardiac end-organ damage. The CAFÉ study on CV outcomes confirmed those findings.

In summary, all of the cited studies exploring the particular viscoelastic properties of the vascular system voluntarily focused on medical symptomatology and therapeutics in specific clinical hypertensive situations. Their results now represent a call for action. Technology is now available to determine serial hemodynamic patterns in the first stages of hypertension, to use vascular age in decision about treatment, and to measure central BP as a target for drug therapy. Nowadays, all these procedures should be used more widely. Moreover, corrections for sex and BP variability should be examined and the major role of older age warrants investigation (Figure 2).
ACKNOWLEDGMENTS

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


