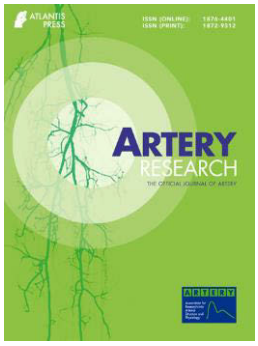

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Thirty-five years of clinical works on arterial stiffness and wave reflections in hypertension

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Introduction

I started my medical studies around 1957. I was resident in Paris between 1962 and 1966 and decided during this period to become nephrologist. At the end of 1966, I began to learn this specialty in the department of Pr Milliez, Broussais hospital. My work was mainly focused on drug treatment of hypertension, chronic hemodialysis and renal transplantation, all subjects leading to studies on sodium, fluid volumes and the kidney. In collaboration with my friend Dr Gérard London, we observed that, at the exception of patients with end stage renal disease (ESRD), intravascular blood volume was never increased in patients with chronic essential hypertension. Then we postulated that, in the absence of absolute increase of intravascular volume, a relative increase in this volume should be expected if the elasticity of the cardiovascular system was reduced.[1] This hypothesis has determined the totality of my research toward a single objective, the elasticity of the cardiovascular system in hypertension. This work was exclusively based on clinical research. I began between 1970 and 1980 by methodological studies and analyses of clinical situations. Thereafter I tried to develop more personal views, affecting mainly histomorphometry, epidemiology, clinical pharmacology and therapeutics of hypertension.

Methodological problems

From 1969 to1982, I tried with G. London and Y. Weiss to solve two methodological questions. The first one was related to the conceptual basis of clinical investigation in hypertensive subjects. The second one was related to the choice of devices enabling to investigate adequately the elasticity of the arterial system.

In order to study the cardiac output level in hypertensive subjects vs. normotensive controls, we tried to conciliate the measurements of cardiac invasive hemodynamic parameters and the use of Guyton's model, here limited to the classical negative feed-back loop characterizing the control of cardiac output, fluid volumes and the kidney in hypertension. We proceeded by different steps. First, using hemodynamic measurements in approximately 1000 subjects, we established 3 clinical protocols: baseline measurements and statistical cross-sectional study; acute rapid volume expansion using iso onkotic dextran in hypertensive patients; repeat hemodynamic studies with long-term follow-up in a population of borderline hypertensive subjects.[2] Second, we modified some equations of the Guyton model in order to use only steady state measurements that we determined successively in the normotensive and the hypertensive populations. Then we showed that, in order to achieve the same cardiac output level in normotensive and hypertensive subjects, several regression coefficients of the hypertensive model should have to be modified, particularly those related to the structural changes of the vessels and to the reduction of arterial and venous vessel elasticity.[3,4] Further, the reduced venous elasticity of hypertensive subjects was shown to have significant consequences on the degree of cardiac hypertrophy, the partition of fluid volumes, and finally renal function. The totality of this original research was published in section IV (volume one) of the book of Laragh and Brenner on hypertension.[5]

Our first work clearly showed that vascular elasticity of both hypertensive arteries and veins was reduced. We then

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focused our research on ''elasticity of large arteries in hypertension'' for several reasons. First, systolic hypertension was responsible for the majority of cardiovascular events in the elderly and therapeutic trials on this subject were just beginning to be developed. Second, antihypertensive drug treatment reduced markedly the occurrence of cardiovascular events through normalization of diastolic blood pressure ($\leq$90 mmHg) but not of systolic blood pressure ($\leq$140 mmHg). Finally we began to understand more adequately the equations characterizing vascular elasticity but we had now to dissociate the role of blood pressure itself from that of pulsatility.[6]

As a first work, we used the Windkessel model to evaluate arterial elasticity. We validated this procedure in hypertensive subjects.[5,6] Because the Windkessel model was not propagative, we decided to use rather pulse wave velocity measurements according to a work developed by Levy et al. and determined between the carotid and the femoral arterial sites.[6] Finally, we focused also our measurements on local determinations of elasticity and diameter, particularly at the sites of brachial and radial arteries, carotid artery, and even, thoracic aorta and femoral artery.[6–9] Visiting our friend Dr Tarazi in Cleveland, we noticed by chance that an engineer working in Broussais hospital (my hospital), Mr Peronneau, had developed a device enabling to determine brachial artery diameter and distensibility using velocity procedures. We validated this device which was then used in clinical research.[8] Later, with the major help of Pr Struijker-Boudier and Rahn in Maastricht (The Netherlands) and Pr Brunner in Lausanne (Switzerland), we participated to the validation of novel devices investigating carotid and radial arteries, using echotracking procedures developed by Pr Hoeks and used by Pr Van Bortel in Maastricht.[7] Measurements of intima-media thickness were obtained in parallel for the carotid and the radial arteries. The latter was developed originally in my department.[9] Finally, we became the first laboratory in the world to measure routinely and non-invasively arterial stiffness and its numerous varieties (compliance, distensibility and incremental elastic modulus) in humans. We worked frequently with the help of Pr Michael O'Rourke from Sydney (Australia), particularly in order to measure local pulse pressure and evaluate central wave reflections transcutaneously by tonometry. Several publications ensued, summarized in the textbook of hypertension by Pr Swales.[10]

Large arteries' structure and function

Together with our friend Pr B. Levy, we determined in Wistar Kyoto and spontaneously hypertensive rats (SHR) the curve relating compliance to transmural pressure established ''in vivo in situ''. At the higher values of transmural pressure (corresponding to the presence of collagen fibers), isobaric compliance was identical in normotensive and hypertensive rats. At a lower transmural pressure, isobaric compliance was lower in hypertensive than in normotensive rats, even after poisoning vascular smooth muscle by potassium cyanide. This finding pointed to the role of structural vascular changes in the mechanism of reduced compliance in hypertension. However, our most original result was the response to de-endothelialization. The loss of endothelium caused an increase in carotid diameter and distensibility, less pronounced in hypertensive than normotensive animals.[11] This experience showed for the first time that, in the presence of endothelium, powerful vaso-constrictive mechanisms contribute to maintain a normal carotid elasticity through their equilibrium with nitric oxide bioactivity.

Thereafter, we compared the mechanical behavior of in situ rat carotid arteries under both static and dynamic conditions, using static transmural pressures ranging from 50 to 200 mmHg. The static pressure—diameter relationship was shifted to higher values of diameter in the SHR, mainly because of a larger unstressed carotid diameter in hypertensive rats.[12] In contrast, carotid compliance and distensibility were similar under dynamic conditions, studied close to the in vivo pulse pressure. We 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.[12] Similar results were found in hypertensive men at the site of carotid and radial arteries even in the presence of vascular hypertrophy.[13,14]

All these findings were shown in human and rat models and were obtained in the presence of a single cardiovascular risk factor: hypertension. Reductions in compliance and/or distensibility independently of mean blood pressure were further observed in the presence of several other cardiovascular risk factors such as aging, obesity, diabetes mellitus, metabolic syndrome, peripheral arterial disease, and most prominently ESRD. In humans, arterial stiffness seemed, in fact, to increase with the degree of endothelial dysfunction and therefore, the number of risk factors involved.[15]

In patients with ESRD undergoing chronic hemodialysis, clinical studies by London et al. have shown that blood pressure (BP) is mainly represented by systolic hypertension and associated with increased aortic stiffness and disturbed wave reflections.[16] Such alterations were independent of mean arterial pressure 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 causes and mainly cardiovascular (CV) mortality.[17] A therapeutic trial in ESRD patients has shown that long-term BP reduction resulting in a significantly improved CV survival is observed mainly in those patients showing adequate BP and aortic stiffness control, particularly in the presence of salt and water restriction associated with angiotensin-converting enzyme inhibition (ACEI).[18] In contrast, patients with appropriate BP reduction but maintaining elevated aortic stiffness have a worse prognosis.[18]

Pulsatile arterial hemodynamics as independent predictors of CV risk

Such studies have shown for the first time that brachial PP, aortic PWV, and even in a higher extent, central PP and wave reflections were independent predictors of CV risk, mainly in the elderly.

In a French study from 1989 including normotensive and untreated hypertensive adults, a pulsatile-component index, defined as a strong correlate of brachial PP, was derived by principal-components analysis from SBP and DBP measurement.[19] An association was found between the pulsatile-component index and electrocardiographic evidence of left ventricular hypertrophy. During a 10 years follow-up, the pulsatile-component index was independently associated with an increased risk of death from coronary artery disease, but not from stroke. The relationship was found consistent for women over 55 years of age, indicating for the first time that PP was an independent CV risk factor.[19] In another prospective study evaluating hypertensive subjects, Alderman et al. in New York confirmed the results in men and women.[20]

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 of age, brachial PP was a stronger CV risk factor than SBP alone for myocardial infarction in populations of hypertensive individuals.[20,21] The best predictor 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 artefact caused by the correlation between SBP and PP.[19–22] A longitudinal study showing that, during 20 years follow-up, subjects with higher CV mortality were those where SBP rose and DBP declined, and their CV mortality rate was significantly higher than that for those whose SBP and DBP both increased.[22] Finally, brachial PP was shown to be an independent predictor of CV risk in subjects with ESRD and/or diabetes mellitus.[17,23] In a population of 19,083 normotensive or hypertensive men followed for 20 years, Benetos et al.[24,25] not only confirmed that elevated brachial PP was a strong predictor of myocardial infarction but also that this predictive value was observed even in a normotensive population, especially in men over 55 years old, and particularly under antihypertensive therapy.[23,25]

Based on patients with ESRD, epidemiologic studies identified three predictors of CV mortality and for overall mortality: aortic PWV, age, and duration of hemodialysis. After adjusting for confounding variables, the odds ratios for PWV (>12 m/s) were 5.6 [95% CI 2.3–15.5] for CV mortality.[17] In contrast, identifying predictive factors contributing to essential hypertension is more complex because long-term longitudinal studies with aortic PWV measurements are difficult to conduct, mainly because of mobility of young patients. However, the CV risk calculated from Framingham equations can partly resolve this difficulty. In a study on 530 hypertensive subjects, the CV risk assessed using 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].[26] Results of longitudinal studies confirmed that aortic PWV is a significant and independent predictor of CV risk, more potent than PP itself.[27,28]

Finally, aortic PP is expected to be more relevant to the evaluation of CV risk than brachial PP, because it is closer to the heart, coronary arteries and carotid arteries, which are the most important sites of CV events. In ESRD patients, aortic PWV and carotid wave reflections and/or mainly central PP were shown to predict independently CV mortality.[29] The finding was confirmed in elderly subjects with hypertension.[30] A consensus was established regarding the validity of central pulse pressure as predictor of CV risk.[30]

Studies in clinical pharmacology and therapeutics

Since clinical and epidemiological studies indicated that large arteries may be a major target for antihypertensive therapy, it was important to show that drug therapy in hypertensive animals can really modify the structure and function of arterial vessels.[31] Although such an effect was easily demonstrated using long-term drug treatment, it was more difficult to determine whether the reversibility of large artery changes was due to BP reduction itself, to an effect of each antihypertensive agent on the large artery wall or to a combination of both factors. Therefore, a set of experiments was performed on this subject, using ACE inhibitors, angiotensin II AT_1 receptor blockers or selective aldosterone antagonists.[23] We showed in animal models that: (1) the regression of aortic hypertrophy was influenced by the BP reduction alone, whereas the reduction of collagen content in the arterial wall was independent of BP reduction; (2) the reduction of collagen content in the aortic wall was due to the blockade of AT_1 receptors or mineralo-corticoid receptors and not to bradykinin; (3) the blockade of AT_1 receptors or mineralo-corticoid receptors was associated with reduction of stiffness of wall material, independent of changes in BP and/or wall stress, a finding predominantly observed in the presence of low sodium diet.[32–34]

In hypertensive humans, it was important to show in a first attempt that arteries were not passive conduits but involve vaso-active responses independent of BP changes. Using double-blind studies, we showed for the first time, that, despite BP reduction (which is able to reduce passively arterial diameter) various antihypertensive agents were able to dilate muscular peripheral arteries, thereby demonstrating in vivo their active relaxing effects.[35] A more difficult issue was to show that antihypertensive agents were able also to increase compliance and distensibility independently of (and in association with) BP changes.[36] In a first step, we showed that some antihypertensive agents, e.g. propranolol, dihydralazine or diuretics, were unable to increase compliance and distensibility despite an adequate BP reduction.[6,36] In a second step, we clearly demonstrated in long-term follow-up that ACE inhibitors increased arterial compliance and distensibility of peripheral muscular arteries and/or improved carotid wave reflections independently of BP changes.[31,37]

This important aspect was demonstrated in the Reason study.[37] This study was the first long-term study investigating the interactions between on the one hand PP, arterial stiffness and wave reflections and on the other hand drug treatment and end-organ damage (cardiac mass) in hypertensive subjects. The ACEI perindopil (Per) associated with low-dose indapamide (Ind) was compared for 1 year of treatment with the beta-blocking agent atenolol. For the same DBP and MBP reduction, Per/Ind lowered SBP and PP more than atenolol. We showed for the first time that the reduction was more

pronounced in central (carotid artery) than in peripheral (brachial artery) arteries. While the two-drug regimens lowered PWV equally, only Per/Ind reduced the augmentation index, which quantified wave reflections.[6] In addition, Per/Ind reduced cardiac hypertrophy more than atenolol, and that reduction was associated with a reduction in carotid wave reflections, indicating their role on cardiac end-organ damage. These findings were confirmed by the CV outcome data in the CAFÉ study.[38]

In summary, these studies based on the visco-elastic properties of the vascular system have been voluntarily focused on medical semiology and therapeutics in clinical situation. Whether this simple approach may have consequences in more basic science cannot be predicted from the present works and requires a personal choice from younger generations.[23,39]

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