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Editorial

A reappraisal of clinical research on arterial stiffness in hypertension in France

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Introduction

Although studies on the definition of hypertension focus almost exclusively on systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements, they frequently target renal and cardiovascular outcomes, with investigations into sodium balance, fluid volumes, and kidney function. Essentially, they have shown that, with the exception of patients with end-stage renal disease (ESRD), total intravascular blood volume is not increased in chronic hypertension. Mean circulatory pressure is greater in these populations. It was therefore postulated that the viscoelastic properties of the cardiovascular system were disturbed in hypertensive individuals, thus implying the presence of increased aortic stiffness in this population.[1] This hypothesis was initiated in France between 1970 and 1980 based primarily on methodological investigations in the United States. Thereafter, specific targets of related research interest were highlighted, mainly epidemiologic data on pulsatile arterial hemodynamics, kidney structure and function, vascular remodeling, clinical pharmacology, and therapeutic design.

Hypertension and Cardiac Output Levels

Initially, two important issues were addressed[2–4]: the conceptual basis of clinical investigation in hypertensive individuals compared to normotensive controls and features of cardiac output (COP) in patients with essential hypertension. The primary objective was to assess COP levels in hypertensive versus normotensive individuals; the main difficulty was reconciling clinical data with the invasive measurements of cardiac hemodynamic parameters from the Guyton model, which was the most widely used conceptual basis to describe the cardiovascular system in pathophysiology. The Guyton model was restricted to the classic negative feedback loop characterizing the control of COP, fluid volumes, and the kidney in subjects with normal blood pressure (BP) or hypertension. Investigations proceeded successively.

First, hemodynamic measurements from approximately 1000 individuals were used to establish clinical protocols to determine baseline measurements of COP and corresponding statistical cross-sectional analyses. These studies investigated the effects of acute, rapid blood-volume expansion under iso-oncotic infusion of dextran in hypertensive patients and performed long-term hemodynamic investigations of a large population of borderline hypertensive patients.[4] The studies concluded that COP levels remained largely within normal ranges in hypertensive individuals.

Second, several equations of the Guyton model were adapted to clinical situations to clarify ''steady-state'' hemodynamic measurements in humans.[2–4]

To obtain the same COP levels in normotensive and hypertensive individuals, several Guyton model coefficients had to be modified, particularly those related to structural changes of the vasculature, of arterial and venous vessel elasticity, and of endothelial function (Figure 1).[2–6] Changes in the viscoelastic properties of large vessels in hypertensive individuals were shown to significantly affect the extent of cardiac hypertrophy, the distribution of fluid volumes, and the reduction in renal function.[7]

Finally, human and rat studies corroborated our findings on vessel viscoelastic properties and highlighted the role of such alterations on a particular cardiovascular risk factor: hypertension. Human and rat studies corroborated our findings highlighting the existence of one single specific cardiovascular risk factor: hypertension. Reduced arterial stiffness (AS) (compliance and/or distensibility) was also observed, independently of BP levels, in the presence of other cardiovascular risk factors including advanced age, obesity, diabetes mellitus, metabolic syndrome, peripheral arterial disease, and above all, ESRD.[8–10] Particularly in humans, AS appeared to increase significantly with the

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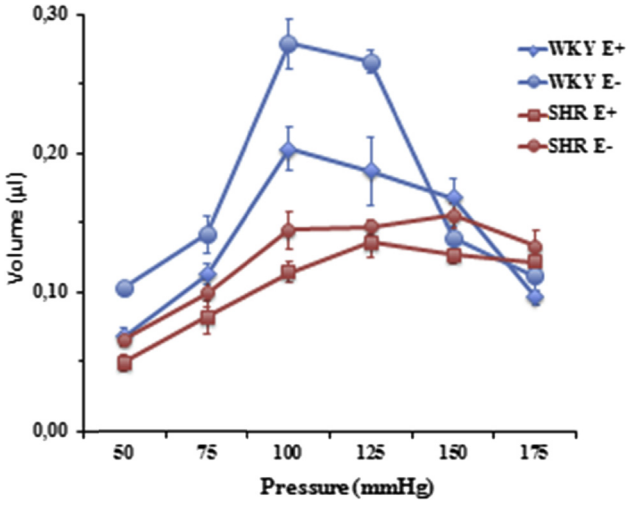

Figure 1. Effects of endothelium removal on carotid volume (and compliance) in normotensive and hypertensive rats (mean ± SD) as a function of transmural pressure. Note that, after endothelium removal, carotid volume is reduced to a greater extent in normotensive than in hypertensive rats. SD, standard deviation; SHR E+, spontaneously hypertensive rats with intact endothelium under control conditions; SHR E−, spontaneously hypertensive rats with damaged endothelium; WKY E+, Wistar Kyoto normotensive rats with intact endothelium under control conditions; WKY E−, normotensive rats with damaged endothelium. Reproduced from Levy et al,[5] with permission.

degree of endothelial dysfunction, and therefore, the number of risk factors involved.[11]

These studies demonstrated that factors characterizing vascular elasticity were consistently modified in hypertensive arteries and veins, suggesting the presence of increased large artery wall stiffness, which was primarily observed when hemodynamic parameters were assessed using the Guyton model.

In the 1980s, we focused on large arteries in hypertension[12] because (1) systolic hypertension, a major consequence of increased aortic stiffness, was known to be responsible for most cardiovascular events, particularly in the elderly; (2) antihypertensive drugs were seen to dramatically reduce cardiovascular events by normalizing DBP (≤90 mm Hg), whereas SBP was still inadequately modified by drug therapy; and (3) equations describing the vascular system, and particularly AS, were the new focus of studies in systolic hypertension. The role of mean BP therefore had to be dissociated from that of pressure pulsatility and vessel characteristics.[13]

Buffering Function of Large Arteries in Hypertension

In cardiovascular physiology, the Windkessel model has long been the only way to adequately assess the buffering function of large arteries in humans. It defines the ability of large arteries to accommodate the volume of blood ejected from the ventricles, storing part of the stroke volume during systole and draining this volume during diastole, thus ensuring continuous perfusion of peripheral organs and tissues. Our group validated this model both in normotensive and hypertensive subjects.[7,13] This was the basis of our understanding of increased AS in hypertension.

The Windkessel model was not a propagative model. We therefore suggested using pulse wave velocity (PWV) measurements to assess aortic stiffness instead of the Windkessel model.[13] Our reasoning was one of the fundamental principles of pathophysiology, that is, that pulse waves travel faster in stiffer arteries. PWV was thus determined between carotid and femoral artery sites. Other vessel properties and diameter parameters were also measured, particularly on the brachial, radial, carotid, and/or femoral arteries, and even thoracic aorta sites. However, only carotid-femoral PWV was shown to be a significant independent predictor of cardiovascular risk.[14]

Safar et al developed devices to determine human aortic and brachial artery diameter and distensibility; they were validated, and carotid-femoral (ie, aortic) PWV was used for the first time in clinical research.[15] Other novel devices were developed and validated for carotid and radial artery diameter measurements using echo-tracking procedures.[16] Carotid and radial artery wall intima-media thickness could be measured concurrently. Most of these techniques were developed at the Broussais hospital (Paris, France),[15,17] which became one of the first medical institutions in the world to routinely and noninvasively assess AS and its numerous derivatives (compliance, distensibility, and incremental elastic modulus) in humans.

In collaboration with Michael O'Rourke (Sydney, Australia), we conducted studies on pulse pressure (PP) and wave reflections. These parameters suggested that the morphology of any pulse wave results from the summation of incident (forward-traveling) and reflected (backward-traveling) pressure waves.[18] Increased PWV subsequently became a widely accepted index of cardiovascular risk, largely influenced by age (Figure 2).[19] More recently, ambulatory variations of such parameters have been investigated and need long duration vessel studies.[20]

Pulsatile Arterial Hemodynamics as Independent Predictors of Cardiovascular Risk

In this report, brachial PP, aortic PWV, and, to an even greater extent, central PP and wave reflections are independent predictors of cardiovascular risk, particularly in the elderly and in the presence of increased aortic stiffness. One recent study even suggests that PP assimilates the effects of age and sex with all-cause mortality more effectively than mean arterial pressure (MAP).[21]