Publications:

- More than 350 publications in English peer-reviewed journals, including more than 250 original articles in: American Journal of Cardiology, American Heart Journal, American Journal of Hypertension, American Journal of Physiology, British Journal of Pharmacology, Cardiovascular Research, Circulation, Circulation Cardiovascular Genetics, Circulation Research, Clinical Research, Drugs, European Journal of Pharmacology, Hypertension, Journal of the American College of Cardiology, Journal of Cardiovascular Pharmacology, Journal of Cellular and Molecular Cardiology, Journal of Clinical Investigation, Journal of Hypertension, Journal of Vascular Research, Lancet, Neurology, PNAS, Stroke…

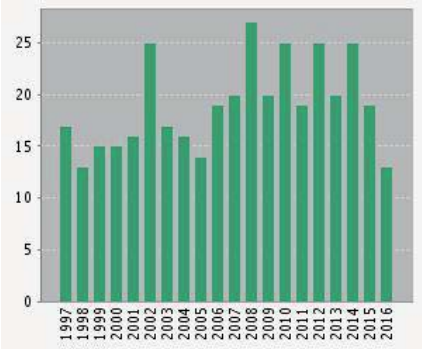
- More than 20 book chapters in English textbooks

- More than 50 articles, reviews or book chapters in French

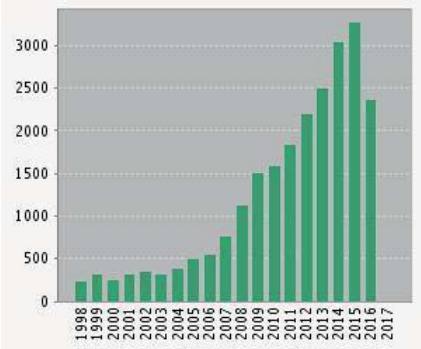
- More than 300 invited lectures at International Meetings

Total number of citations: 22 990
Index h: 63
Oct 17, 2016; ISI web of Science,
AU=laurent s* and AD=paris

Annual number of publications



Annual number of citations



5 most cited articles

1. Mancia G, de Backer G, Cifkova R, Dominiczak A, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, **Laurent S**, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder R, Struijker Boudier HA, Zanchetti A. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens*. 2007;25:1751-1762. *Times Cited: 3,139*

2. L**aurent S**, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588-605. *Times Cited: 2,187*

3. **Laurent S**, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001, 37: 1236-1241. *Times Cited: 1,955*

4. 2007 Guidelines for the management of arterial hypertension - The task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC) By: Mancia, Giuseppe; De Backer, Guy; Dominiczak, Anna; et al. *Eur Heart J* 2007; 28: 1462-1536 *Times Cited: 1,246*

5. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, **Laurent S.** Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients - A longitudinal study. *Hypertension* 2002; 39: 10-15. *Times Cited: 982*

Teaching activities

National activities

1987-now Teaching courses on cardiovascular pharmacology at Paris-Descartes University

2004-now Teaching courses on clinical pharmacology, drug development and methodology of clinical trials at Paris Descartes Medical School, School of Pharmacy and University of Sciences

2004-now Master courses on the pharmacology of the arterial system at
- Paris-Descartes University, Schools of Medicine and Pharmacy
- Paris XIII University, School of Pharmacy
- Paris Diderot University, School of Medicine

International activities

2005-2015 Master courses on “Arterial hypertension and cardiovascular risk factors”, organized by the European Society of Hypertension – ESH, during both Winter Schools and Summer Schools, in several countries, including France.

2012-2016 Annual Master Course on « Early Vascular Aging », organized by Porf. Pedro Cunha, Minho University, Portugal

2013-2015 Annual Master Course on « Arterial structure and function », organized par Prof. Michael Olsen, University of Southern Denmark – USD

2008-2015 Intensive Master Course on Hypertension, organized in Paris (2008), Prague (2009), Krakow (2009), Valencia (2010), Prague (2014) and Gdansk (2015)

General framework of the research work

During the last 25 years, my group has worked in the field of arterial disease and their pharmacological treatments. Our general aim was to provide novel pharmacological treatment for preventing the complications of polygenic or monogenic arterial disease. This was based on a precise description of the arterial phenotype, leading to a better understanding of the pathogenesis of the arterial disease, thus suggesting novel cellular and molecular targets. It initially required a multidisciplinary approach, from basic research to epidemiology and large clinical trials, with a special input on technological development. Four years ago, in order to maintain our leadership in a rapidly expanding field, we decided to focus mainly on clinical studies.

Our clinical approach of the pathogenesis and pharmacology of arterial disease followed the usual steps of translational research:

1. *The technological development of "high-tech" apparatus*, using either high sensitivity pressure and flow sensors, high resolution ultrasounds, and recently MRI, capable of measuring noninvasively *in vivo* in humans, with a very high precision, the geometrical and functional properties of large arteries, at different levels of the arterial tree. We worked in collaboration with engineers and acted as expert consultant for several manufacturers. We assessed several of these apparatus, made recommendations for improvement, and validated them against reference methods.
2. *The selection of noninvasive, precise, and reproducible arterial parameters*, for pharmacological studies in humans. These parameters measured either arterial function (i.e. arterial stiffness, central blood pressure) or remodeling (i.e. arterial wall thickness and enlargement). This selection was oriented by…
    3. …*basic research in animals and pathophysiological studies in animal models* of hypertension or monogenic disease in order to better understand the mechanics of the arterial wall, its cellular and molecular determinants, and better select appropriate drugs for preventing arterial complications.
    4. …*pharmacodynamic studies in animal models* of hypertension or monogenic disease, providing the proof of concept that a drug acting on a specific pharmacological target could modify the arterial phenotype and ultimately prevent complications
5. *The physiological study of normal arterial ageing, and the pathophysiological study* of a variety of monogenic disease (including Marfan, Ehlers-Danlos, and Williams syndromes) and polygenic arterial disease (including hypertension, chronic kidney disease - CKD, and diabetes). These studies allowed showing which parameters could be considered as characteristic of the disease, and their complications: arteriosclerosis (increased arterial stiffness and central BP), atherothrombosis (increased carotid wall thickness and plaque), arterial rupture and dissection (high circumferential wall stress), obstruction by non-atherosclerotic inward remodeling and ischemia (wall thickening and low circumferential wall stress).
6. *Reference values were established,* in order to determine the normal distribution of a given arterial parameter (aortic stiffness, carotid IMT, central BP) in a healthy population, according to age and gender, and their variations depending on CV risk factors.
7. *Epidemiological studies* showed the predictive value of selected parameters (arterial stiffness, central BP, carotid remodeling) for cardiovascular (CV) event (including CV mortality, myocardial infarction and stroke) and renal event (decline in glomerular filtration rate - GFR, dialysis)
8. *Pharmacodynamic studies* followed gold standard methodology of *r*andomized clinical trials (RCTs), in order to compare the effects of a given molecule on a selected arterial parameter, with those of either a placebo or a reference drug.
9. *Ultimately*, *large RCTs were performed to demonstrate that a given molecule*, selected on its ability to modify a given parameter of arterial structure and function, *was able to prevent arterial complications*

International leadership

I. My research group was the first to demonstrate that **arterial stiffness was a strong, independent risk factor,** first in end-stage renal disease patients (1999) then in hypertensives (2001-2003). Following these pioneer studies, more than 19 international studies, involving >20 000 patients with various conditions, confirmed our original findings.

The leadership of my research group in this domain is attested by the following:

1. One of our paper (*Laurent et al. Hypertension 2001*) was classified by the JAMA among the 120 publications of clinical medicine (among 30 cardiovascular publications) the most cited during the 2 months following publication.

2. Two of our papers (*Laurent et al. Hypertension 2001; Boutouyrie et al. Hypertension 2002*) are among the 20 most cited papers in the journal *Hypertension* (Impact Factor 6.87), respectively at rank 2 and 11 (See http://hyper.ahajournals.org/reports/mfc_all_10.dtl). The total of citations of these two papers is above 2,892. These papers are ranked 15th and 49th among the top 100 scientific reports focused on hypertension research during the last century (Oh and Galis, Hypertension 2014;63-641-647).

3. The total of citations of these 2 papers and a third one (Laurent et al. *Stroke* 2003), all on the predictive value of arterial stiffness for CV events, is larger than 3,600.

II. With the *Working Group on Arterial Structure and Function* of the European Society of Hypertension and the *European Network for Non Invasive Investigation of Large Arteries* (ENN-2i-LA) which I lead since 2004, I co-authored **several guidelines aiming at better standardizing the measurement of arterial stiffness and central blood pressure**. The leadership is attested by the following:

1. The « Expert consensus document on arterial stiffness » (*Laurent et al. Eur Heart J 2006*) is the fourth most often cited paper published in *European Heart Journal* (Impact Factor 14.71). http://eurheartj.oxfordjournals.org. This paper has been cited already 2,187 times.

2. The "Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity" (*Van Bortel L, Laurent S et al. J Hypertens 2012*), which updated the 2006 Guidelines, has already been cited 280 times.

III. With the "*Collaboration for arterial parameter measurements*" which I lead since 2008, we established the **reference values for several arterial parameters**, in large collaborative cohorts, including up to 91 588 subjects. I co-authored the following papers on the reference values of

1. - pulse wave velocity (*Boutouyrie et al. Eur Heart J 2010*). This paper has been cited 322 times.

2. - carotid IMT using echotracking system (*Engelen et al. Eur Heart J 2013*)

3. - central blood pressure (*Herbert A et al. Eur Heart J 2014*)

4. - carotid stiffness (*Engelen et al. J Hypertens 2015*)

5. - femoral stiffness (*Bossuyt et al. J Hypertens 2015*)

IV. In clinical pharmacology, my research group was the first to demonstrate that (a) **arterial stiffness and thickness were reduced in parallel by antihypertensive treatment,** but without causal relationship; (b) **arterial stiffness could be reduced independently of blood pressure**

lowering, in response to blockers of the renin-angiotensin system (ACEIs and ARBs) through a dose-dependent direct effect; (c) **beta-blockers** had deleterious effects on central blood pressure and could induce arterial wall stiffening on the long term, surpassing the favorable destiffening effect expected from BP reduction. These demonstrations were achieved through several RCTs, regularly cited:

- the PERICLES study was published in *JACC* (Girerd et al. 1998) and cited 97 times
- the CELIMENE study was published in *Circulation* (Boutouyrie et al 2000) and cited 132 times
- the DAPHNET study was published in *Hypertension* (Tropeano et al. 2006) and cited 80 times
- the BBEST study was published in the *Lancet* (Ong et al. 2010) and cited 66 times
- the EXPLOR study was published in *Hypertension* (Boutouyrie et al. 2010) and cited 79 times
- the *Vascular Mechanisms Study* was published in *Hypertension* (Laurent et al. 2014)

V. This amount of scientific evidence on both the predictive value of arterial stiffness for CV events and the pharmacologic effects of antihypertensive agents has urged the writing group of the "2007 ESH/ESC Guidelines for the Management of Hypertension" to **include arterial stiffness in the evaluation of global CV risk. Arterial stiffness measurement was also listed among the various target organs** to be investigated in order to improve the management of elderly hypertensives and high risk patients. These recommendations were reinforced in the 2013 ESH/ESC Guidelines for the Management of Hypertension. I participated to the Guidelines writing committees of 2007, 2009 and 2013. Particularly, I was in charge of drafting the "arterial system" part of the Guidelines.

VI. My group played an important role in the **development of a new scientific society, named "ARTERY"** - Association for Research into Arterial Structure and Physiology (I was vice – President, then President), and a **new scientific peer reviewed journal, named "Artery Research**". ARTERY Society organizes annual meeting, with 200-400 attendees

For the above reasons, my group acted as a "**reference research group"** in the field of pathophysiology, pharmacology and imaging of the arterial wall. This explains the large number of:

- citations of papers originating from my group or collaborations
- invited lectures at international meetings
- and visiting scientists.

Main scientific results

Our research work concerned arterial disease and their pharmacological treatments. It was enclosed in the general framework of a multidisciplinary research, and it was focused on the pathogenesis and pharmacology of arterial diseases. Our general aim was to provide novel pharmacological treatment for preventing the complications of polygenic or monogenic arterial disease.

We focused on large artery mechanics for several reasons. First, large artery stiffness plays a key role by relaying heart contraction during diastole using elastic energy storage through distension of large proximal arteries, and releasing this energy during diastole. This helps to maintain diastolic blood flow, limits the rise in systolic blood pressure and increases diastolic perfusion of coronary arteries. By maintaining an impedance mismatch between central and peripheral circulations, it favours pressure wave reflection and protects target circulations, such as brain and kidney.

Second, thanks to recent developments in pressure and flow sensors, high resolution ultrasounds techniques, and MRI, it has been possible to describe precisely the phenotype of the arterial tree at various levels: ascending aorta, aortic arch, descending aorta, abdominal aorta, common carotid, brachial, radial, and common femoral arteries. Arterial phenotype can be determined non-invasively, for both arterial function (arterial stiffness, endothelial dysfunction) and remodeling (arterial wall thickness and enlargement), Third, the precise description of the arterial phenotype allows a better understanding of the pathogenesis of the arterial disease, which suggests novel cellular and molecular targets.

I. "High-tech" developments in the non-invasive measurement of arterial parameters

We contributed to the technological development of "high-tech" apparatus, using either high sensitivity pressure and flow sensors, high resolution ultrasounds, and recently MRI, capable of measuring noninvasively in vivo in humans, with a very high precision, the geometrical and functional properties of large arteries, at different levels of the arterial tree. We worked in collaboration with engineers and acted as expert consultant for several manufacturers. We assessed several of these apparatus, made recommendations for improvement, and validated them against reference methods.

Before describing our main scientific results, we believe appropriate to briefly describe the main methods. Our work, and an "Expert consensus statement" on the measurement of arterial stiffness and central BP (*Laurent et al. Eur Heart J 2006*) contributed to popularize these methods and bring them to research centers, and ultimately to the routine clinical ward. Arterial stiffness can be measured at the systemic, regional and local level. We favoured the two later measurements, since they do not require any model of the circulation. Arterial remodeling, by definition, is measured at the local level.

Regional arterial stiffness: Although the theory of measurement of the pulse wave velocity is known for near a century, high precision was obtained only with the development of domestic computers, and largely benefited from the extraordinary development of software for video-games, which largely increased the speed of signal processing. Briefly, carotid-femoral pulse wave velocity (PWV) is accepted as gold standard for directly determining aortic stiffness. cfPWV is usually measured using the foot-to-foot velocity method from various waveforms. These are usually obtained, transcutaneously at the right common carotid artery and the right femoral artery (i.e. "carotid-femoral" PWV), and the time delay (Δt, or transit time) measured between the feet of the two waveforms. A variety of different waveforms can be used including pressure, distension and Doppler. The distance (D) covered by the waves is usually assimilated to the surface distance between the two recording sites. PWV is calculated as PWV = D (meters) /Δt (seconds). As shown in the table at the end of this document, there was recently an important development of novel apparatus, bringing innovation in algorithms and signal process, increasing precision and repeatability.

Local stiffness and arterial remodelling: High-resolution echotracking systems made a "revolution" in ultrasound apparatus, allowing the measurement of arterial diameter of superficial arteries and their pulsatile changes, with a degree of precision which has not been reached until then. Briefly, these apparatus use the radio-frequency (RF) signal to obtain a precision 6 to 10 time higher than with video-image systems, which are limited by the spatial resolution of pixel analysis. Indeed, the precision in determining stroke change in diameter is as low as 1 micron for echotracking systems, whereas it is around 150 microns (i.e. the size of the pixel) with video-image analysers. For absolute distance measurement, the standard deviation extends from 9 to 25 microns for echotracking systems, and from 54 to 60 microns with video-image analysers. Several indices are used to describe the structural and functional properties of blood vessels, non-invasively obtained with ultrasound measurements. The remodeling of the artery is characterized by intima-media thickness (IMT), lumen diameter (D), wall-to-lumen ratio, wall cross-sectional area (WCSA), and circumferential wall stress (calculated as $\sigma\theta$=MBPxD/IMT). The elastic properties of the artery as a hollow structure are assessed through arterial distensibility, determined from the systolic-diastolic variations in arterial lumen cross-sectional area (ΔA) and local pulse pressure (ΔP), as DC=ΔA/A. ΔP. The elastic properties of the arterial wall material are estimated by the Young's incremental elastic modulus (Einc), which takes into account the thickness of the arterial wall, as Einc = [3(1 + A / WCSA)]/DC, (kPa). Calculation of Young's modulus from IMT assumes that the wall is homogeneous and load-bearing.

II. Arterial mechanics in monogenic arterial diseases: predictive value for arterial complications, and pharmacological prevention

We applied the concepts of mechanotransduction and fatigue of biomaterials to vascular tissues, and characterized the phenotype of large arteries in monogenic diseases or the arterial wall in order

- to better understand their pathogenesis,
- to determine the arterial parameters which can be used for monitoring the progression of the disease in patients and predict CV events and mortality, and
- to test the efficacy of cardiovascular drugs, selected for their effects on central pressure and arterial stiffness.

II.1. A major finding is that circumferential wall stress is implied in the pathogenesis of arterial complications in arterial monogenic disease

We could show in patients with vascular Ehlers Danlos (EDSv) and Marfan syndrome (both associated with arterial fragility) that both static and cyclic circumferential stresses were elevated (EDSv), and could contribute to aortic dilatation (Marfan) and arterial dissection and rupture (EDSv). Opposite to these findings, we found that patients with Williams syndrome, pseudoxanthoma elasticum (PXE) and Fabry disease (associated with either obstruction by non-atherosclerotic inward remodeling and ischemia, or stenosis and early atherosclerosis) had decreased levels of circumferential wall stress. We thus hypothesized that an either deficient (EDSv, Marfan) or overactive (Williams, PXE, Fabry) mechanotransduction across the arterial wall could lead to inappropriate changes in arterial thickness and diameter, explaining the type of complications observed in those disease. Defects in mechanotransduction is an important finding, since it restrains the field of research to molecular and

II.2. Vascular Ehlers Danlos syndrome (EDSv)

Patients with EDSv die early from arterial dissection and rupture. We have identified in those patients a specific arterial phenotype associating hypotrophic remodelling with marginally decreased arterial distensibility *(Boutouyrie et al. Circulation 2004).* We set up a multicenter "PROBE" trial, the BBEST study (PHRC 2001, NCT00190411), in which we tested the hypothesis that beta-blocking with celiprolol, a beta-1 antagonist with beta-2 agonist properties, shown to decrease pulse pressure and arterial stiffness in hypertensives (*Boutouyrie et al. Circulation 2000),* could prevent arterial dissection and rupture in this disease (*Boutouyrie et al. Circulation 2004).* Our hypothesis is that the reduction in pulse pressure and heart rate by

celiprolol should decrease the fatigue of deficient collagen III within the wall, thus decrease the likelihood of rupture. This trial has included 53 patients in France and Belgium, with a mean follow-up of 47 months. The primary endpoints (rupture or dissection fatal or not) were reached by five (20%) in the celiprolol group and by 14 (50%) controls (hazard ratio [HR] 0.36; 95% CI 0.15–0.88; p=0.040) (*Ong et al. Lancet 2010*). Celiprolol thus might be the treatment of choice for physicians aiming to prevent major complications in patients with vascular Ehlers-Danlos syndrome.

This study shows that a novel pharmacodynamic approach, based on “high tech” measurement of the arterial system although using a “classical” drug, can lead to the discovery of a very effective protective treatment in patients at high risk of vascular dissection and rupture. Ongoing research focuses on the predictive value of carotid wall stress for vEDS mutation. Although we showed that celiprolol was very effective at preventing cardiovascular events, the mechanism was different from the one expected. Indeed, carotid wall thickness, which was measured every year during the study, proved to increase in the celiprolol group, whereas it did not change in the placebo group, suggesting a profibrotic effect of celiprolol on the arterial wall, likely mediated by stimulation of beta-2 receptors and/or unopposed baroreflex induced alpha-receptor stimulation, involving TGF-β activation.

II.3. Fabry disease: Fabry disease is linked to a deficit in alpha-galactosidase leading to an accumulation of uncleaved glycosphingolipids (GSL) in tissues, mostly nervous system, kidney, heart and arteries. These patients die early of kidney failure and heart failure, because of arterial obstruction and concomitant tissue ischemia. Enzyme replacement therapy (ERT) is available since 2001. Although the reduction in tissue deposit of GSL has been demonstrated, the clinical benefit of ERT is more difficult to prove. Indeed, some precursors and metabolites of GSL may still exert trophic effects despite the reduction in GSL deposit. Our hypothesis was dissociation between the clearance of GSL and regression of target organ damage. We studied the effects of ERT (agalsidase beta, 1 mg/kg/14 days) on arterial and cardiac structure and function during a longitudinal study beginning in 1999, with 4.5±0.4 years follow-up (4 visits) in 30 patients (age: 33±12 years). In addition, we studied 16 untreated Fabry patients during 2.6±1.6 years (2 visits). A sustained reduction in aortic stiffness (-0.56±0.13 m/s/yr, P=0.0002) and left ventricular hypertrophy (LVM measured using MRI: -7.8±2.3 g/m2/yr, P<0.005) and a limited radial artery wall thickening were observed after long-term enzyme replacement therapy (*Collin C et al. Eur J Cardiovasc Prevention and Rehabil 2010*). There was no significant benefit of treatment on carotid hypertrophy. Ongoing research relates to the relationships between (1) aortic root dilation and LVH, measured with MRI, during long term follow-up, and (2) aortic and carotid structure and function.

II.4. Fibromuscular dysplasia: We showed that fibromuscular dysplasia is accompanied by a specific echotracking aspect of the arterial wall, which we named “triple line pattern” (*Boutouyrie et al. J Hypertens 2003*). This demonstrates that abnormalities of the arterial wall could be detected with a high frequency on asymptomatic arteries, although the expression of the disease is focal, targeting mainly renal and cervical arteries. We demonstrated that this trait was transmitted according to an autosomic dominant pattern (Perdu et al. J Hypertens 2007). Ongoing research is now testing the screening value of the triple signal for the positive diagnosis of fibromuscular dysplasia, by comparison with CT scan-angio in a large prospective trial (the PROFILE Study).

II.5. - STAT3 deficiency is responsible for autosomal dominant hyper-IgE syndrome characterized by recurrent bacterial and fungal infections, connective tissue abnormalities, hyper-IgE and Th17 lymphopenia. The prevalence, characteristics and etiology of vascular abnormalities were not described. In collaboration with Necker Enfants Malades (A. Fischer), the radiology team of HEGP (E. Mousseaux, A. Azarine) and the PARCC-INSERM U970 (Z. Mallat), we prospectively screened 21 adults STAT3-deficient patients (median age: 26 years; range 17 - 44) for vascular abnormalities. They were explored with whole-body magnetic resonance imaging angiography, coronary multislice computed tomography and echotracking-based imaging of the carotid arteries. Brain abnormalities (white matter hyperintensities, lacunar lesions suggestive of ischemic infarcts, atrophy) were found in 95% of patients. Peripheral and brain artery abnormalities were reported in 84% of patients, whereas coronary artery abnormalities were detected in 50%. The most frequent vascular abnormalities were ectasia and aneurysm. The carotid intima-media thickness was markedly decreased, with a substantial increase in circumferential wall stress indicating the presence of hypotrophic arterial remodeling in this STAT3-deficient population, compared to age-sex matched controls. Systemic

inflammatory biomarker levels correlated poorly with the vascular phenotype, whereas there was a significant correlation between the extent of systemic vascular abnormalities with carotid remodelling. These data (*Chandesris et al. Circulation Cardiovascular Genetics 2011*) suggest that the defect in tensile stress-mediated mechanotransduction translates into a subsequent propensity for arterial dilation and tortuosity in many arterial sites.

III. Arterial mechanics in polygenic arterial disease: predictive value for cardiovascular events and pharmacology of their prevention

The understanding of the pathogenesis of rare vascular disease helped us to generate new hypotheses regarding the pathogenesis of arterial complications occurring in various conditions such as hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease

III.1. Novel concepts in arterial mechanics

Our group has been at the origin of (or significantly contributed to) several important concepts in arterial mechanics, which are summarized below.

III.1.1. Arterial stiffness is an independent marker of cardiovascular risk

We were the first to demonstrate that arterial stiffness was a strong and independent CV risk factor in hypertensives (see above; *Laurent et l. Hypertension 2001; Boutouyrie et al. Hypertension 2002; Laurent et al. Stroke 2003*). Following these pioneer studies, more than 19 international studies, involving >20 000 patients with various conditions, confirmed our original findings, and showed the predictive value of aortic stiffness for fatal and non-fatal CV events in various populations having different levels of CV risk: general population, hypertensive patients, elderly subjects, type 2 diabetic patients and patients with end-stage renal disease. Seventeen longitudinal studies totalizing 15,877 subjects with a mean follow-up of 7.7 yrs were included in a recent meta-analysis (*Vlachopoulos et al. JACC 2010*) which showed, for one standard deviation (SD) increase in pulse wave velocity, a risk ratio of 1.47 [1.31-1.64] for total mortality, 1.47 [1.29-1.66] for CV mortality, and 1.42 [1.29-1.58] for all-cause mortality.

III.1.2. Arterial stiffness is an “imaging” biomarker

Among “imaging” biomarkers, arterial stiffness in general and aortic stiffness in particular can be considered as a measure of the cumulative influence of CV risk factors with aging on the arterial tree, having limited acute variability (mainly depending on blood pressure) and enough inertia to reflect the integrated damage of the arterial wall (*Laurent et al. Hypertension 2012*).

III.1.3. Pulse pressure is a stronger determinant of arterial remodelling than mean blood pressure

We demonstrated (*Boutouyrie et al. Circulation 1999, Boutouyrie et al. Circulation 2000*) that central pulse pressure was a strong determinant of arterial dilatation and thickening, independent of mean pressure, and that regression of central pulse pressure was accompanied by a parallel improvement of lumen diameter and wall thickness.

III.1.4. Arterial stiffness contributes to the “large/small artery cross talk”

In addition to the damaging effect of local PP on large arteries (see above), elevated PP can stimulate hypertrophy, remodelling (increased media-to-lumen ratio), or rarefaction in the microcirculation, leading to increased resistance to mean flow. In recent studies, our group and others showed a close relationship between microvascular damage in the heart, brain, retina and kidney and either PP or arterial stiffness. Indeed, we showed significant relationships between central PP and either glomerular filtration rate (GFR), microalbuminuria, or white matter lesions; between arterial stiffness and either GFR, urinary albumin, and white matter lesions; and between carotid stiffness and GFR. Although not all these relationships are independent of confounding factors, there is a large amount of evidence for linking the pulsatility of BP to target organ damage.

We raised the concept of “large/small artery cross-talk” (*Laurent et al. Hypertension 2009; Laurent and Boutouyrie, Circ Res 2015*), to explain the vicious circle between small and large artery damage. This mutually reinforcing arterial damaging can be exemplified by the following sequence: (a) increased wall-to-lumen ratio and rarefaction of small arteries are major factors for an increase in mean BP; (b) the higher mean BP in turn increases large artery stiffness, through the loading of stiff components of the arterial wall at high BP levels; (c) the increased large artery stiffness is a major determinant of the increased PP, which in turn damages small arteries in the heart, brain, retina and the kidney, as seen above, and favours the development of left ventricular hypertrophy, carotid intima-media thickening and plaque rupture. These various types of target organ damage have been shown to be related with CV events. Thus, the cross-talk between small and large artery exaggerates arterial damage, following a vicious circle. Antihypertensive treatment, by acting both on small and large arteries, could reverse this vicious circle into a “virtuous” circle: the pharmacological arterial remodelling at both levels should be able to reduce central PP, thus target organ damage and CV events. As we will see below, not all pharmacological classes are equal in this respect.

III.1.5. Early vascular aging can be detected by “imaging” biomarkers, such as arterial stiffness and remodelling

As aging is a common denominator to many chronic disease manifestations, such as CV disease, type-2 diabetes or cancer, we proposed, with Peter Nilsson (Malmo, Sweden) that early vascular aging (EVA) could be a useful concept to better guide clinical investigations in subjects at increased CV risk (*Nilsson et al. Hypertension 2008; Nilsson et al. J Hypertens 2013*). This could be the case in individuals with marginally elevation of classical risk factors or with a strong family history of early CVD manifestations. There might also be a special link between adverse growth patterns in fetal or early post-natal life (the “mismatch” growth hypothesis) and the EVA syndrome, as recently summarized.

Vascular aging in general, and EVA more specifically, can be investigated non-invasively through the measurement of arterial stiffness, central blood pressure, carotid intima media thickness, and endothelial dysfunction. These parameters, which can be considered as "imaging” biomarkers, may be more predictive than "circulating" biomarkers, like hs-CRP, and show a better additional prediction when coupled to classical CV risk scores. We therefore proposed that clinical research should focus on the validation of “imaging” biomarkers as surrogate end-points for CV risk reduction in large clinical trials.

III.1.6. Surrogate value of arterial stiffness should be demonstrated in large clinical trials.

Arterial stiffness is currently considered as a putative “surrogate” end-point for CV events, but it has not been proven. Although aortic stiffness has already met with various criteria, as recommended by the AHA (Hlatky MA et al. Circulation 2009), it has not yet been shown that the use of arterial stiffness measurement improves clinical outcomes, especially when tested in a randomized clinical trial. To answer to this question, we started a RCT, the SPARTE study, with financial support from PHRC (*Programme Hospitalier de Recherche Clinique 2011*). This RCT is described below (*Laurent et al. Hypertension 2012*).

III.1.7. In hypertensives, arterial wall hypertrophy is not accompanied by an increased arterial stiffness, and is rather an adaptive phenomenon aimed at limiting the passive increase in arterial stiffness with BP.

For years, it was intuitively accepted that an increased stiffness of the arterial wall material explained the increased stiffness of large arteries in hypertensives. We could demonstrate that this was not the case. Arterial hypertrophy in hypertension was accompanied by normal (or even decreased) arterial wall stiffness, both in human and in animal models of hypertension (SHR). We raised the concept of an adaptive phenomenon aimed at limiting the passive increase in stiffness with blood pressure, and designed the following studies, in order to identify the molecular and cellular determinants of arterial stiffness *(Laurent et al. Hypertension 1995; Lacolley et al. Am J Phys 1995; Lacolley et al. Hypertension 1995; Lacolley et al. Br J Pharmacol 1995; Mourad et al. Hypertension 1998; Laurent et al. Hypertension 2005)*

III.1.8. The cellular and molecular determinants of arterial stiffness are much more complex than elastin and collagen, and involve cell-matrix organisation and attachments

We identified genes/proteins implied in large artery remodeling and stiffening, by using novel technologies along three research directions:

- First, thanks to novel echotracking devices, we studied in humans the arterial phenotype of monogenic diseases characterized by defect in components of large artery structure, mainly extracellular matrix components (see paragraphs II.1 to II.4)

- Second, we transferred these techniques in small animals invalidated for genes of the arterial wall (desmin, alpha-1 integrin, initiated in INSERM EMI107, then continued through collaboration with INSERM U684 – P Lacolley).

- Third, we used the novel DNA-chips technology (1999-2003) (Laboratory of Physiological Genomics, Harvard Medical School, Boston, Pr V. Dzau; and then Laboratoire de Physiologie Génomique - CNRS UMR 6097, Sofia-Antipolis, Dr P. Barbry, chips with 25 000 human genes), to establish the gene expression profile of aortic samples obtained during coronary bypass surgery, in patients with stiff or distensible aortas.

Our main findings are summarized below:

- **Circumferential wall stress is implied in the pathogenesis of arterial complications in arterial monogenic disease** (detailed in paragraph II.1)

- **Arterial wall stiffness is more dependent on qualitative changes of arterial wall components than quantitative modifications in absolute content or density.**

  With Patrick Lacolley (now head of INSERM U684 unit), we have shown that the structural three-dimensional organization of the arterial wall components allowed the artery to maintain their mechanical properties, despite the elevated level of stress (*Laurent et al. Hypertension 2005 for review*). This new organization implies enhanced cell-cell and cell-matrix interactions through fibronectin, and a better repartition of stress around fenestrations into the elastic laminae *(Bezie et al. ATVB 1998; Bezie et al. Hypertension 1998; Boumaza et al. Hypertension 2001).* These results, initially considered as provocative, have been acknowledged by many international research teams.

- **The gene expression profile of arterial tissues with contrasted stiffness levels (low vs high) may help to identify candidate genes and target proteins, and suggest new pharmacological approaches to reduce arterial stiffness independently of blood pressure reduction.**

  We applied the "GeneChip Microarray" technology to aortic tissues originating from patients scheduled for coronary artery bypass graft. The gene expression profile of patients with high arterial stiffness was compared to patients with normal arterial stiffness, adjusted for confounding factors (age, BP, smoking, cholesterol, diabetes…). We demonstrated that genes differentially expressed between stiff and distensible aorta, belonged in 2 major functional categories: “cell structure/motility” and “signaling/communication with the extracellular matrix” (*Durier et al. Circulation 2003*), reinforcing our hypothesis raised above. Moreover, differentially expressed genes were involved in VSMC contraction and in extracellular matrix organization, including proteoglycans (decorin, ostéomoduline, dermatopontin).

  A similar work was performed in patients with mild-to-moderate chronic kidney disease (CKD). We showed that differentially expressed genes were involved in the regulation of actin filaments (CAP1, CAPZA1, ARPC3, moesin), migration (APOD, ODC1) and organization of VSC (mainly lumican). Genes implicated in vascular calcifications were not differentially expressed between patients with and without CKD. The presence in the arterial wall of proteins encoded by most of differentially expressed genes was confirmed by immunohistochemistry (*Fassot et al. J Hypertens 2008*). These abnormalities are consistent with the arterial enlargement and stiffening reported in patients with CKD (*Briet et al. Kidney Int 2006*).

III.2. Recent findings in arterial mechanics in polygenic disease

Consistently with our previous findings, we showed

- The predictive value of aortic stiffness for the functional outcome after acute stroke.

We showed that aortic stiffness, measured as carotid-femoral pulse wave velocity 7 days after an acute stroke, was predictive of the functional outcome at 90 days, independently of the classical NIHSS score on admission and presence of previous stroke (*Gasecki et al. Stroke 2012*). Similar results were observed for the functional outcome at discharge (*Gasecki et al. Atherosclerosis 2012*). Because of these studies and previous related ones from our lab, we have been invited to participate to an AHA/ASA statement for healthcare professionals (*Gorelick et al. Stroke 2011*).

- The predictive value of aortic stiffness for CV events in patients with mild-moderate CKD.

We demonstrated that aortic stiffness (cfPWV) but not arterial remodelling had predictive value for CV events in patients with mild-moderate CKD (*Karras et al. Hypertension 2012*).

- The predictive value of arterial stiffness and remodelling for the decline in renal function and CV events in patients with chronic kidney disease - CKD

We demonstrated for the first time the predictive value of arterial remodelling for the progression of renal dysfunction in patients with CKD before dialysis. A cohort of 170 patients with CKD, included in the NEPHROTEST study, was studied during a longitudinal follow-up of 4 years (PHRC 2003 and ANR 05-PCOD-027). We demonstrated (Briet et al. JASN 2011) that a maladaptive remodeling (reduced IMT and increased circumferential wall stress) and increased pulse pressure of the carotid artery predicted CKD progression and end stage renal disease (ESRD). Indeed, in multivariate logistic regression analyses, urinary albumin to creatinine ratio (UACR) and circumferential wall stress were independent determinants for CKD progression (OR 2.23 [1.29-3.83], P=0.03; 1.53 [1.05-2.25], P=0.02 respectively). Circumferential wall stress and carotid pulse pressure remained independent determinants of end stage renal disease (HR 1.40 [1.12-1.75]. One could hypothesize that maladaptive remodeling of large arteries could impact the transmission of pulse pressure with a stronger intensity further down the microcirculation. Excessive pulsatility could induce damage to the microcirculation such as capillary rarefaction and increased small arteries stiffness; these damages could be greater in patients with increased circumferential wall stress value.

We also demonstrated that aortic stiffness (cfPWV), but not arterial remodelling had predictive value for CV events (*Karras et al. Hypertension 2012*).

- The predictive value of arterial stiffness and remodelling for subclinical brain damage

White matter lesions (WML) are considered good intermediate endpoints for stroke and cognitive decline. In the COVADIS study (Dijon, Christophe Tzourio (PI) and Carole Dufouil, INSERM U 708), we took advantage of an automated determination of WML at MRI to study the relationships between arterial stiffness and WML. In multivariable analyses adjusted for age, total brain volume, MBP, heart rate and diabetes, aortic stiffness was significantly related to higher periventricular WMLs volume only in males (odds ratio of being in 3rd tertile of WML volume [per 1 SD increase in PWV]: 1.48; 95% CI: 1.10 to 2.02; P<0.05) but not in females (OR: 1.04, P=0.71).

- The predictive value of arterial stiffness and remodelling for sudden death remains to be demonstrated.

This hypothesis will be tested in the PPS3 study *(Paris Prospective Study 3),* which is a prospective study, initiated by Xavier Jouven (Inserm U970), including 10,000 subjects, aged >50 years, from the general working population. The objective is to identify the determinants of sudden death in a follow-up of 10 years. Patients had a complete clinical and biological workup, a 3 hour-long Holter ECG, and additional arterial investigations, under the responsibility of our team: echotracking analysis of the carotid geometry and function, and the neural component of carotid baroreflex, i.e. occurring “downstream” the carotid distension. The neural component of the baroreflex function (neural-BRS) can be determined non-invasively and with enough repeatability by recording simultaneous during 5 minutes both the distension waveforms of the carotid diameter (echotracking) and HR (RR interval). 10,000 subjects have already been investigated during the last 4 years, and the longitudinal analysis is planned in 6-10 years from now. In the meantime, we plan several cross-sectional

analyses, (a) to determine the relationship between the mechanical properties of the common carotid artery (generally accepted to be similar to those of the carotid bulb) and neural-BRS, (b) to determine whether, in some population such as patients with chronic kidney disease (CKD) or type 2 diabetes (T2D), the lower baroreflex sensitivity is due to altered mechanical properties of the carotid artery, or altered neural component, and (c) to establish normal (i.e. no CV risk factor) and reference (i.e. CV risk factors, but no diabetes) values of neural-BRS (see above).The major longitudinal analyses will concern the predictive value of carotid parameters (mainly stiffness) and neural-BRS for sudden death.

III.3. Reference values for arterial parameters

With the development of various techniques measuring arterial stiffness and remodeling under different physiological conditions and in various disease, it became urgent (a) to provide recommendations for gold standard measurement (**see above section I**), (b) equivalence between methods, and (c) reference values for interpreting the data.

III.3.1. Reference values for arterial stiffness. The measurement of arterial stiffness is listed among those recommended by the ESH Guidelines for the Management of Hypertension. A threshold of 12 m/s pulse wave velocity (PWV) has been proposed by these Guidelines, above which the risk is largely increased. However, this threshold may not apply similarly to a 30 and 70 years old patient. We thus established normal (i.e. no CV risk factor) and reference (i.e. CV risk factors, but no diabetes) values for arterial stiffness in 16,867 subjects originating from 13 different centres across eight European countries *(Boutouyrie et al. Eur Heart J 2010).* This study is the first to establish reference and normal values for PWV, combining a sizeable European population after standardizing results for different methods of PWV measurement. We took advantage of the constitution of the European Network for Non Invasive Investigation of Large Arteries (ENN-2i-LA), gathering data from 13 different centres across eight European countries, in which PWV and basic clinical parameters were measured. Of the 16 867 subjects, 11 092 individuals were free from overt CV disease, non-diabetic and untreated by either anti-hypertensive or lipid-lowering drugs and constituted the reference value population, of which the subset with optimal/normal blood pressures is the normal value population.

III.3.2. Reference values for carotid IMT. We also determined normal and reference values for common carotid (CCA) thickness (IMT) using the probably most accurate method at present, the echotracking technology. This study was made possible through collaborations between U970 and Maastricht (C. Stehouver and I. Ferrreira). CCA IMT data obtained by echotracking on 24,871 individuals originated from 24 research centres worldwide. Individuals without CVD, cardiovascular risk factors (CV-RFs) and BP-, lipid- and/or glucose-lowering medication constituted a healthy sub-population (n=4,234) used to establish sex-specific equations for percentiles of IMT across age. With these equations we generated IMT Z-scores in different reference sub-populations, thereby allowing for a standardized comparison between observed and predicted ('normal') values from individuals of the same age and sex (*Engelen L, et al. Eur Heart J 2013*). Ongoing research will use data of patients originating from the above cohort, coupling changes in diameter and local pulse pressure, allowing to calculate carotid stiffness [as 1/(distensibility)1/2] and Young's elastic modulus (i.e. taking into account IMT).

III.3.3. Reference values for central blood pressure. A similar approach was followed to establish normal and reference values for central BP. This study was made possible through collaborations between U970 and the London Imperial College (K. Cruickshank). Central SBP and PP values, obtained on 91,588 individuals (including 27,658 healthy individuals) by aplanation tonometry or related methods, and originating from 54 research centers worldwide, have been recently published (*Herbert et al. Eur Heart J 2014*). The next step will address the issue of the determinants of the discrepancies between brachial and central BP, in order to compare the role of classical CV risk factors and techniques.

III.3.4. Reference values for carotid and femoral stiffness. They have been published in *Journal of Hypertension*.

IV. Pharmacology of the arterial wall: observational studies and randomized clinical trials

We describe below the main finding of several RCTs, which have been designed to answer to issues raised by physiological and pathophysiological studies, described above. These RCTs have been gathered in this section, to better demonstrate how our pharmacological approach was a consequence of pathophysiological findings.

IV.1. PERICLES study: antihypertensive treatment is associated with a reduction in arterial wall hypertrophy and carotid stiffness.

In the late 1990s, although novel high resolution apparatus allowed measuring arterial wall hypertrophy and stiffness, two consequences of hypertension on peripheral arteries, little pharmacodynamics studies had been done. The PERICLES study *(Girerd et al. JACC 1998)* tested whether a diuretic- or an ACEI–based treatment can reduce arterial wall hypertrophy of a distal muscular (i.e. conducting) medium-sized artery, the radial artery, and the stiffness of a proximal large elastic artery, the common carotid artery. We studied 77 elderly hypertensive patients, who were randomized to receive 9 months of double-blind treatment with perindopril (2 to 8 mg/day) or the diuretic combination of hydrochlorothiazide (12.5 to 50 mg/day) plus amiloride (1.25 to 5 mg/day) after a 1-month placebo washout period. During treatment, blood pressure and arterial variables changed to the same extent in both groups. We showed that, after a 9-month treatment, systolic, diastolic and pulse pressures and radial artery wall thickness, mass and thickness/radius ratio decreased significantly ($p< 0.01$), whereas carotid compliance increased ($p <0.001$). The improvement in carotid compliance was related to the reduction in mean arterial pressure ($p < 0.01$).

IV.2. CELIMENE study: The effect of PP lowering on IMT reduction was observed at the site of an elastic artery but not at the site of a muscular artery in hypertensives

As detailed above, local pulse pressure (PP) is an independent determinant of arterial wall hypertrophy, stronger than mean blood pressure (MBP). The CELIMENE study was designed to assess whether a beta-blocker-based or an ACEI-based treatment was able to reduce carotid artery wall hypertrophy through a reduction in carotid PP rather than by lowering mean BP and whether the influence of local PP reduction could also be detected at the site of a muscular artery, the radial artery. 98 essential hypertensive patients were randomized to 9 months of double-blind treatment with either celiprolol or enalapril. After 9 months of treatment, mean BP, carotid PP, and intimal-medial thickness (IMT) decreased significantly, with no difference between the 2 groups. The reduction in carotid PP but not in MBP was a major independent determinant of the reduction in carotid IMT. Radial artery IMT and PP decreased significantly with both treatments. However, the reduction in radial artery IMT was not related to the changes in radial artery PP. Thus, the effect of PP lowering on IMT reduction was observed at the site of an elastic artery but not at the site of a muscular artery (*Boutouyrie et al. Circulation 2000*).

IV.3. DAPHNET and "VASCULAR MECHANISM" studies: blockers of the renin-angiotensin system can reduce arterial stiffness independently of the decrease in blood pressure in hypertensives

Whether ACEIs and ARBs can effectively remodel the arterial wall independently of BP reduction, through their antihypertrophic and antifibrotic effects, remains a matter of controversy.

In the **DAPHNET study** (*Tropeano et al. Hypertension 2006*), we demonstrated a direct dose-dependent and BP-independent effect of angiotensin-converting enzyme inhibitors on arterial stiffness. In this mechanistic study, we used an experimental design in which patients responding to 1 month treatment with 4 mg perindopril were randomized double-blind to either 4

mg perindopril or 8 mg perindopril for 6 months. We determined carotid distensibility with echotracking and applanation tonometry at baseline and after the 7-month treatment period in 57 essential hypertensive patients with type 2 diabetes. After 7 months treatment, 24hBP significantly decreased, with no significant difference between 4 mg and 8 mg perindopril. Carotid distensibility increased more after 8 mg perindopril compared with 4 mg perindopril. Carotid internal diameter and elastic modulus were significantly lower after 8 mg perindopril compared with 4 mg perindopril, independent of BP reduction. These results also suggest that long-term administration of high doses (8 mg) of perindopril is required to improve carotid structure and function in hypertensive patients with type 2 diabetes.

We further tested this hypothesis in the **"VASCULAR MECHANISM" study**, by using three doses of an angiotensin receptor blocker (ARB), olmesartan, in a phase 3, multi-centre, double-blind, randomized, parallel-group study. 133 subjects with hypertension and metabolic syndrome were assigned to 3 treatment groups and received either OM 20 mg (n=44), OM 40 mg (n=42), or OM 80 mg (n=47) once a day according to a force-titration design during a 1 year period. PWV significantly decreased (P<0.001) with time in each group, with no significant time-dose interaction, despite a tendency for a smaller effect of 20 mg, compared to 40 and 80 mg at W52. When the 40 and 80 mg doses were combined (40/80 mg vs 20 mg), there was a tendency (p=0.0685) for a time-dose interaction in PWV reduction. After adjustment to changes in 24hMBP, a significant BP-independent reduction in PWV was observed: PWV decreased by -0.61 m/s at W52 (p=0.0066) after 40/80 mg, whereas the non-adjusted reduction was -1.33 m/s (p<0.0001). Most carotid parameters were improved along with BP reduction, and at W52 significant reductions were observed for carotid PP (-7.15 mmHg) and internal diameter (-0.217 mm), indicating a chronic inward arterial remodeling. Patients receiving the highest dose of OM (40 and 80 mg) were shifted towards both a low elastic modulus and a low wall stress, indicating an improvement in the intrinsic elastic properties of the arterial wall material. These data suggest that 40 and 80 mg Olmesartan are able to significantly remodel and destiffen the arterial wall during long-term treatment, partly independently of 24hMBP, compared to 20 mg (*Laurent et al. Hypertension 2014*)

These findings are consistent with an observational study (**SARGENT study**) showing, in 97 patients with treated essential hypertension under conditions of routine clinical practice, that PWV significantly decreased from 14.2±4.2 to 11.1±2.5 m/s (P<0.01), whereas MBP did not change significantly. In multivariate analysis, the reduction in PWV between the initial and final visits was dependent not only on baseline PWV value and the reduction in MBP, but also on the number of antihypertensive drugs and the follow-up duration (*Ait Oufella et al. J Hypertens 2010*).

IV.4. EXPLOR study: The beta-blocker atenolol, even administered in combination with an ARB, is less effective than a calcium-channel blocker for reducing central BP in hypertensives. The LIFE, ASCOT, and ACCOMPLISH studies strongly suggest that combination therapies should be best associated with a RAS blocker (either ACEI or ARB) and a calcium channel blocker. However, the effects of such combination on central BP are unknown. In addition, betablockers are less effective than other pharmacological classes of antihypertensive agents to reduce central BP, and prevent stroke (LIFE, ASCOT, and meta-analyses). We studied the reduction in central systolic BP in response to amlodipine/valsartan combination vs amplodipine/atenolol combination. This French multicenter randomized double-blind trial, which started in January 2008, included 560 hypertensives, receiving either the amlodipine/valsartan combination or the amlodipine/atenolol combination for 6 months. We demonstrated (*Boutouyrie et al. Hypertension 2010*) that the amlodipine-valsartan combination decreased central blood pressure (SBP and PP) and AIx more than the amlodipine-atenolol combination. Altogether, the EXPLOR and BBEST studies, the LIFE and ASCOT studies, the meta-analyses on betablockers, and the pharmacodynamics studies in animals, suggest that beta-blockers exert a deleterious profibrotic effect on the arterial wall, limiting the reduction in arterial stiffness and central BP, and thus impairing the prevention of cerebrovascular complications.

IV.5. BBEST study: the findings of this multicenter "PROBE" trial, have been detailed above. Briefly, in patients with Ehlers-Danlos syndrome, and fragile arteries, the beta-blocker celiprolol is able to reduce the incidence of primary endpoints (rupture or dissection, fatal or not),

compared to control treatment (hazard ratio [HR] 0.36; 95% CI 0.15–0.88; p=0.040) (*Ong et al. Lancet 2010*). Celiprolol thus might be the treatment of choice for physicians aiming to prevent major complications in patients with vascular Ehlers-Danlos syndrome.

IV.6. Conclusion of paragraphs IV.1 to IV.5:

- Blockers of the renin-angiotensin system (either ACEI or ARB) are drugs of choice for reducing the arterial damage of hypertensive patients, i.e. arterial stiffening and wall thickening.
- The effects of ACEI and ARB are partly BP-independent.
- Betablockers should be avoided in hypertensives when there is no compelling indication (CHD, CHF, AF).

Our results, associated with important pharmacodynamic studies performed by other research groups, contributed to establish the “ranking” of antihypertensive drugs to be preferentially used in hypertension, in order to prevent arterial damage. We wrote several reviews and book chapters on this topic.

IV.7. SPARTE study: Improvement of clinical outcome by measuring aortic stiffness

Arterial stiffness is currently considered as a putative surrogate end-point for CV events. A large number of studies showed that it indeed met with various criteria, as recommended by the AHA (*Hlatky MA et al. Circulation 2009*). However arterial stiffness has fulfilled only 4 of the 6 criteria. Particularly, it has not yet been shown that the use of arterial stiffness measurement improves clinical outcomes, especially when tested in a randomized clinical trial.

To answer to this question, we set up a French multicenter RCT, with financial support from PHRC (*Programme Hospitalier de Recherche Clinique 2011*) and *Fondation de la recherché en Hypertension Artérielle* (2011). The aim of the SPARTE study is to show that a therapeutic strategy targeting the implementation of international guidelines PLUS the normalisation of BP (BP < 140 and 90 mmHg) PLUS the normalisation of arterial stiffness (measured every 6 months) (PWV group) reduces CV and renal events to a significantly greater extent than the sole implementation of the Guidelines for the management of hypertension (conventional group, with PWV measurement at baseline and every 2 years).

The main criteria is a combined one including one among the following events, either fatal or non fatal: stroke (except TIA), coronary events (MI, angioplasty, coronary bypass), PAD (angioplasty, bypass, amputation), hospitalisation for CHF, aortic dissection, doubling of plasma creatinine, end-stage renal disease, sudden death.

The therapeutic strategy is derived from the various pharmacodynamic studies that we performed during the last 20 years (PERICLES, CELIMENE, DAPHNET, BBEST, EXPLOR, Vascular mechanism). It follows a sequential approach:

- Use maximal recommended doses of ACEIs or ARBs as first step treatment.
- In a second step, use combination therapy with CCBs.
- Use diuretics in combination therapy, either as an alternative to CCBs in second step or as triple therapy in third step.
- Use, as fourth step, vasodilating beta-blockers (VD-BB) or spironolactone
- In parallel, correct all CV risk factors according to ESH-ESC Guidelines, and reinforce treatment (hypolipidemic drugs, glucose lowering drugs, antiplatelets) if secondary prevention.

This RCT, which has been launched in September 2013, aims at including 1,500 hypertensives at medium/high/very high CV risk and no T2D, followed for 4 years according to a PROBE design (*Laurent et al. Hypertension 2012*).

V. Novel methods and developments in imaging technology of the arterial wall

As detailed above, we contributed to the technological development of "high-tech" apparatus, using either high-sensitivity pressure and flow sensors, high-resolution ultrasounds, or recently MRI, capable of measuring noninvasively *in vivo*, with a very high precision, the geometrical and functional properties of large arteries, at different levels of the arterial tree. The studies, described below, were only possible because of the interface between skilled clinicians, arterial investigation experts (echotracking, MRI), industrial developers, and mostly experts of mechanics-physics (M Zidi and I Masson, Paris; P Segers, Gent), who could modelize and implement high end-physic models for non-linear, viscoelastic, and compressible materials in real geometry. Active collaborations among the "EUREKA Artmed" network and the "EUREKA CARUS" network, helped at improving both the hardware and software for investigation methods. Our research center has been clinical advisory and validation center for several new techniques.

V.I. Mechanics of plaque rupture and arterial wall dissection

These studies focused on the mechanics of the carotid artery wall, for various reasons. The carotid is a privileged site for the development of atherosclerotic plaques. The common carotid artery is a superficial artery, accessible to non-invasive measurements on a large portion (4 cm length.). Its elastic behavior is close to that of the thoracic aorta, although the various determinants of carotid stiffening may be different from the determinants of aortic stiffening (*Paini et al. Hypertension 2007*).

Our main technological developments in biomechanics were the following:

V.1.1. Measurement of compressibility. The arterial wall is generally thought to be non-compressible. However, measurements with echotracking shows that this compression is not negligible, and may deeply influence the repartition of stress within the wall, exposing some zones to markedly increased stress (*Boumaza et al. Hypertension 2001*; *Boutouyrie et al. Hypertension 2001)*

V.1.2. Determination of longitudinal bending stress. The objective is to provide a detailed characterization of the mechanical parameters along the carotid plaque, including not only the circumferential forces, but also the longitudinal ones, in order to determine which type of carotid wall behaviour is at high risk of plaque rupture. Very recent methodological developments of echotracking technology (WallTrack system), including the use of a 128 RF lines multiarray, provided a novel system (ArtLab), which allowed us benefiting from both the advantages of the echotracking technology and those of classical B-mode ultrasound systems. It was thus now possible to determine, with high resolution (10 µm) and high reproducibility, the intima-media thickness of the carotid artery, its internal diameter, and the pulsatile changes in diameter and pressure, for any length of an arterial segment in the range of 0.1-4.0 cm, at the site of the common carotid artery. Using this technology, we observed (*Paini et al. Hypertension 2006; Paini et al. Stroke 2007*) two types of longitudinal gradients of distension, that we named pattern A (outward bending strain, i.e. a larger radial strain at the level of plaque than at the level of adjacent CCA) and pattern B (the opposite, i.e. an inward bending strain). Pattern B patients were more often dyslipidemic and type 2 diabetic than pattern A patients.

We then examined the relationship between the observed mechanical properties (ultrasounds) and the composition of plaque at high resolution MRI (HR-MRI). Complex plaques (i.e., American Heart Association [AHA] stages IV to VIII) at HR-MRI more often displayed a reduced strain than the simple plaques. HR-MRI verified complex plaques were associated with an outer remodeling upon echotracking, and had a lower distensibility than adjacent CCA. An outer remodeling was observed in plaques with a lipid core at HR-MRI and was more frequent in symptomatic carotids. These findings indicate that the longitudinal mechanics of "complex" plaques follows a specific pattern of reduced strain. They also suggest that reduced strain, associated with an outer remodeling, may be a feature of high-risk plaques *(Beaussier et al. JACC Cardiovasc Imaging 2011).*

V.1.3. Determination of media power. Intima-media thickness (IMT) measured through ultrasound scanners is a popular marker of early atherosclerosis; however atherosclerosis

primarily develops within the intima, not the media. Thus IMT might not always represent a true atherosclerosis load since increased thickness of the media might also contribute to its increase. Until now, it was considered impossible to discriminate between the intima and the media with percutaneous ultrasound scanners. Improvements in the treatment of information, quality of probes and new techniques such as echotracking have dramatically improved the quality of image and precision of measurements. Echotracking has divided by a factor 10 the resolution of ultrasound scanners, opening the possibility to measure intima thickness. In partnership with ESAOTE Netherlands, we developed a new software taking advantage of stored radiofrequency matrix of the common carotid artery obtaineed in 2,500 subjects, to study the media power. The media power is the ultrasound reflectivity within the media (the media is defined as the hyporeflective zone between blood intima interface and media adventitia interface). We showed that “intima thickness” is only dependent on carotid diameter, whereas media power is lower in obese subjects and higher in hypertensives patients. Ongoing research will extend feasibility to the whole cohort (10,000 subjects followed 10 years). The prognosis value of these parameters will be prospectively studied.

V.2. Novel development in high-frequency imaging: Ultrafast imaging of the arterial wall

We developed a collaboration with ESPCI (Ecole Supérieure de Physique Chimie Industrielle de Paris; M. Fink, M. Pernot) in order to apply a novel method of ultrafast imaging to the arterial wall mechanics. The stiffness of the arterial wall can be determined directly, without any assumption concerning blood pressure, by measuring pulse wave velocity by ultrafast echo and wall thickness by high resolution echotracking. The radiation force of the ultrasonic beam, which is focused on the arterial wall, induces a transient shear wave (#10 ms) whose propagation is tracked by ultrafast imaging. The large and high-frequency content (100 to 1500 Hz) of the induced wave enables studying the wave dispersion, which is shown experimentally in vitro and numerically to be linked to arterial wall stiffness and geometry. By repeating the acquisition up to 10 times per second (theoretical maximal frame rate is #100 Hz), it is possible to assess in vivo the arterial wall elasticity dynamics. Ongoing research focus on the relationship between arterial wall hypertrophy and stiffness, “revisiting” our old findings with novel technology.

V.3. Study of heart-vessel coupling by combining Magnetic Resonance Imaging and echotracking

The objective is to combine the expertise of Prof. Elie Mousseaux in the MRI assessment (patented software, Department of Cardiovascular imaging, Hopital Pompidou) of cardiac and aortic geometry and function, with our expertise in the measurement of arterial parameters, to assess heart-vessel coupling with a precision which has never been reached until now, and to incorporate additional parameters. MRI allows determining aortic arch geometry (length, diameters, height, width, and curvature), aortic arch function (local aortic distensibility and arch PWV), and LV volumes and mass. By combining radial tonometry and MRI, it is possible to determine the aortic pressure wave and flow, respectively, and calculate complex parameters of arterial geometry and mechanics, such as aortic impedance and inertance. The research group of E. Mousseaux has also done pioneering works using cine MRI, to estimate regional mean transition times and radial velocities, and thus detect of silent myocardial infarction and fibrosis, and LV diastolic function.

The objectives of this ongoing research are (a) to better differentiate the effects of aging on the aorta, peripheral arteries, and LV diastolic function, in healthy and disease populations (particularly patients with hypertension, metabolic syndrome and type 2 diabetes), (b) to detect silent myocardial infarction and fibrosis, and LV diastolic function in selected populations, and (c) to investigate the effects of classical and novel antihypertensive drugs on heart-vessel coupling.

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