Introduction to the Fifth International Workshop on Structure and Function of Large Arteries

Edward D. Frohlich, Michel E. Safar

From February 3 through February 5, 2005, the Fifth International Workshop on Structure and Function of Large Arteries was held in Paris. As with the preceding Workshops, the program and participants were a resounding success and, as organizers of the Workshop, we are delighted with the attendance, the presentations, discussions, and, especially, with the manuscripts that were contributed for publication in this issue of Hypertension. The proceedings of the past 3 (of the 4) Paris workshops were also published in this journal, and we are particularly pleased with the responses of those many new workers in this field who have been stimulated and contributed to the extant knowledge in this growing field. With much satisfaction, since publication of these workshops, the number of papers dealing with this subject cited in PubMed has increased remarkably. Evidence of worldwide interest clearly reflects the remarkable stimulus of the Parisian workers in this field and the obvious impact made by publication of these workshops (Figure). This does not minimize the fundamental conceptual and technical developments in this field by others, but this figure reflects the impact made by these 4 Workshops. In addition, the stimulus is no doubt exacerbated by the contemporary interest generated by the vast problem of isolated systolic hypertension in the elderly and the convergence of each of these events. Furthermore, we are most grateful to Servier Pharmaceuticals for their unrestricted educational support for each of these Workshops.

The scientific program of this Workshop was introduced by a keynote discussion on vascular stiffening by David A. Kass (Johns Hopkins Medical Institutions, Baltimore, Md), who provided an exciting and erudite overview of the subject integrating the pathophysiological alterations induced by vascular stiffening. This presentation set the pace for the Workshop and, happily, it is available as the lead article of the workshop. After this introductory lecture, Edward G. Lakatta (Gerontology Research Center, Baltimore) provided an insightful report that emphasized an important concept that has a direct bearing on the discussions by Drs Kass and Lakatta. Thus, in the presentation by Dr Frohlich, the increased arterial pressure (systolic, diastolic, mean, and pulse pressure) had stabilized in adult SHR at age 16 weeks and did not increase further to age 80 weeks. However, aortic distensibility significantly decreased as pulse wave velocity increased more impressively. During this period of salt-loading, left ventricular and aortic relaxation and stiffness were improved by angiotensin II receptor blockade, whereas arterial pressure remained unchanged. The details of this presentation are not published herein because they have been published very recently elsewhere. Nevertheless, these findings have a direct bearing on the discussions by Drs Kass and Lakatta. Furthermore, these new workers in this field who have been stimulated and contributed to the extant knowledge in this growing field. With much satisfaction, since publication of these workshops, the number of papers dealing with this subject cited in PubMed has increased remarkably. Evidence of worldwide interest clearly reflects the remarkable stimulus of the Parisian workers in this field and the obvious impact made by publication of these workshops (Figure). This does not minimize the fundamental conceptual and technical developments in this field by others, but this figure reflects the impact made by these 4 Workshops. In addition, the stimulus is no doubt exacerbated by the contemporary interest generated by the vast problem of isolated systolic hypertension in the elderly and the convergence of each of these events. Furthermore, we are most grateful to Servier Pharmaceuticals for their unrestricted educational support for each of these Workshops.

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tricular diastolic functions also improved. Thus, even though the arterial structural and functional changes associated with the aging process have been considered to be “normal” in the aging person or experimental normotensive or naturally occurring hypertensive rat, arterial pressure may increase further and aortic mechanics may become significantly impaired. Furthermore, these findings indicate that whereas certain drugs may preferentially improve these age-related alterations, other therapeutic agents may not have these beneficial effects.

Two other factors participating in the mechanical aspects of arteries were discussed by Patrick Lacolley (Paris) and Robinson Joannides (Rouen). The former presentation was concerned with the critical role of dense plaques, collagen, and adhesion modules on the elastic aspects of arteries. The latter investigator’s presentation provided evidence for the role of the endothelial hyperpolarizing factor in regulating the caliber of human peripheral conduit arteries.

There were several subsequent sessions to the Workshop. The first was devoted to epidemiological aspects of pulse pressure and arterial stiffness. One presentation, by Stanley Franklin (Los Angeles), concerned the mechanisms underlying systolic hypertension in young people. In that presentation, the pathophysiological alterations were very different from those described for isolated systolic hypertension in the elderly. In the younger patients with systolic hypertension, there was an increased cardiac output associated with the pressure elevation; these changes stand in striking contrast with those in elderly patients who have an increased total peripheral resistance and less distensible large arteries. Additionally, the younger patients were, for the most part, overweight if not obese. These findings had been shown previously to occur in juvenile “borderline” or labile hypertension and in obesity. Thereafter, Van Bortel (Ghent) presented an overview of the various means for noninvasive assessment of arterial pulse pressure. This presentation was followed by 2 discussions, by Coen Stehouwer (Maastricht) and Cristina Giannattasio (Monza), on arterial stiffness in the metabolic syndrome and large arterial structure and function in young, normotensive, healthy subjects with a strongly positive family history of type 2 diabetes mellitus, respectively. Both of these metabolic conditions are of increasing importance and have been associated with premature cardiovascular morbidity and mortality. It was of considerable interest that even apparently healthy offspring of diabetic patients seem to be characterized by altered large vessel mechanics. These findings are of considerable importance when one considers that the patients studied were young and healthy. As we are aware, many large-scale epidemiological studies have been using methodologies that assess the thickness of carotid or branchial arteries as a marker of disease, more notably early atherosclerosis (vide supra). Thus, in Lakatta’s earlier presentation, the Workshop was impressed that this assessment of large vessels may not entirely reflect atherosclerotic changes; they may simply reflect arterial changes associated with the aging process, per se. However, in the presentation (from Monza), one finds carotid arterial changes occurred in apparently healthy and young individuals. Thus, one must consider that these changes represent the earlier alterations produced by a heritable disease.

This concept was discussed in greater detail in the next session on newer aspects of arterial stiffness. In that session, Athanase Benetos (Paris) discussed the genetic predetermination of arterial stiffness in twins and he clearly demonstrated a genetic predetermination for abnormal arterial distensibility. After that presentation, Kennedy Cruikshank (Manchester) followed through on this concept by discussing maternal and infant influences on aortic pulse wave velocity. Mary Roman, of Cornell Medical Center (New York), then discussed arterial stiffness in chronic inflammatory diseases, focusing primarily on the collagen vasculitides. Olivier Hanon (Paris) and Wilmer Nichols (Gainesville, Florida) added further “grist for the mill” by providing the relationships between arterial stiffness and cognitive decline in elderly subjects and the increase in arterial stiffness, wave reflection amplitude, and left ventricular afterload in over-
weight individuals, respectively. Hence, the entire field is learning a great deal more about how a multiplicity of variables influences the development of abnormal large arterial mechanics in health and disease.

In the next session, newer technical approaches involved in the analysis of arterial pulse waveforms. In this segment of the Workshop, Alberto Avolio (Sydney) presented an application of self-organizing maps to characterize the arterial pulse waveform, and James Cameron (Melbourne) discussed brachial and aortic arterial pressure and wave velocity as predictors of the central systolic pressure using brachial hypertension as a screening for central hypertension. Then, Charalampos Vlachopoulos (Athens) and Michael Bots (Utrecht) each discussed how various lifestyle factors can adversely affect aortic stiffness and wave reflections in middle-aged and elderly men. The former presentation concerned the effects of coffee, tea, and chocolate, whereas the latter discussed those of alcohol. Lastly, Daniel Hayoz (Lausanne) discussed how diabetic neuropathy might be a more important determinant of baroreflex sensitivity than carotid arterial elasticity in patients with type 2 diabetes mellitus.

Having presented a widely varying number of associated morbid and lifestyle factors that influence larger arterial function, the next session focused on alterations in large arterial structural composition in health and disease. Thus, Mahmoud Zureik (Lille) discussed how certain serum tissue inhibitors of metalloproteinases affect their structure and function, and John Cockcroft and Ian Wilkinson (Cambridge) demonstrated that basal nitric oxide locally modulates endothelial function and, hence, arterial stiffness, in vivo. Bruno Pannier (Floury-Merogis) then showed that vasodilation may be independent from endothelial functional influences on arterial stiffness in patients with end-stage renal disease (ESRD). Isabelle Lartaud (Nancy) then opened the Workshop’s thinking about how vascular calcification may predispose development of renal failure. Other studies dealing with vascular calcification were discussed later but, finally in this session, Martin Hausberg (Muenster) introduced to the Workshop the role of certain cardiovascular therapeutic agents (ie, valsartan and metoprolol) on large arterial function in hypertensive patients.

Next, the Workshop dealt further with arterial calcification and stiffness. This subject was reintroduced by Sharon Moe (Indianapolis), who carefully discussed the potential cellular mechanisms influencing vascular calcification in chronic kidney disease. The topic was discussed in further depth by Ralf Westenfeld (Aachen), Paolo Raggi (Tulane, New Orleans), and Gerard London (Floury-Merogis). They discussed the impact of fetuin-A phosphate and uremia on the development of cardiovascular calcification, the progression of coronary arterial calcification, and the risk of myocardial infarction, and the inter-relationships between arterial calcification and bone turnover in ESRD, respectively. To our way of thinking, the finding of arterial calcification has been said to be an important early predictor of subsequent cardiovascular morbidity and mortality. However, at present, the precise mechanisms involved in explaining the underlying mechanisms for these severe endpoints of arterial calcium deposition are poorly understood and certainly demand study.

The next session focused on macrocirculation and microcirculation and disease. In these presentations, Harry Struijker Boudier (Maastricht), Tarek Francis Antonios (London), Jean-Jacques Mourad (Bobigny Cedex), Peter De Leeuw (Maastricht), and Albert Mimran (Montpelier) each discussed other factors and diseases on these circulation. Thus, Struijker Boudier discussed the transient aldosterone on the development of hypertension involving an intrarenal microvascular action. Antonios introduced the concept of vascular rarefaction of cutaneous capillaries in patients with essential hypertension and the relationship with ambulatory blood pressures, salt intake, and the renin-angiotensin system, and Mourad discussed aortic pulse pressure, microvessels, and atherosclerotic structural alterations in coronary arteries. However, de Leeuw and Mimran focused their work on the kidney and discussed the continuous relationship between the degree of obstruction and the intrarenal microcirculation in hypertensive patients with renal arterial stenosis, and the role of elevated pulse pressure and its association with low renal function in elderly patients with isolated systolic hypertension, respectively.

Finally, the last session of the Workshop dealt with the subject of therapeutics and the pharmacological aspects associated with arterial stiffness. To this end, Gary Mitchell (Holliston, Mass) discussed the pulsatile hemodynamic effects of angiotensin-converting enzyme inhibition or vasopeptidase inhibition in hypertension drawing on a larger multicenter therapeutic trial. Bonwyn Kingwell (Melbourne) discussed angiotensin-converting enzyme inhibition on large arterial stiffness and matrix protein deposition in both clinical and cell culture studies. Jay Cohn (Minneapolis) focused on the integration of a number of clinical, demographic, and indices of large arterial stiffness on predicting long-term morbidity and mortality in apparently normal individuals.

As one overriding thought about this very stimulating and wide-ranging Workshop, we were tremendously impressed about one very important feature. When these important Workshops were first organized, there was little interest around the world in the role of the large arteries in health and disease. Today, the number of patients with hypertension has dramatically increased in all nations. This, no doubt, reflects the importance of isolated systolic hypertension and the associated increased arterial pulse pressure in these elderly people. The importance of this clinical problem provided additional impact on the necessity for clinicians and investigators to understand more clearly the underlying mechanisms of disease associated with arterial stiffness, the influences of co-morbid diseases and lifestyle alterations, and the promise of existing and future therapies on reducing the increased morbidity and mortality associated with this problem. To this end, we hope that this Workshop serves to whet the appetite of those with new and renewed interests and in those already aware of the tremendous potential for future research in this broad area.
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