Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases

Michel E. Safar
Michael F. O'Rourke
Edward D. Frohlich
Editors

Springer

Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases

Michel E. Safar • Michael F. O'Rourke
Edward D. Frohlich
Editors

Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases

Springer

Editors
Michel E. Safar, MD
Hôtel-Dieu Hospital Diagnosis
and Therapeutics Center
Paris Descartes University
Paris
France

Edward D. Frohlich, MD, MACP, FACC
Department of Cardiology
Ochsner Clinic Foundation
New Orleans, LA
USA

Michael F. O'Rourke, MD, DSc
St Vincent Clinic and Hospital
University of New South Wales
Victor Chang Cardiac Research Institute
Darlinghurst, Sydney
New South Wales
Australia

ISBN 978-1-4471-5197-5 ISBN 978-1-4471-5198-2 (eBook)
DOI 10.1007/978-1-4471-5198-2
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2014946213

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Contents

Contributors

Davide Agnoletti, MD, PhD Diagnosis and Therapeutics Center, Hôtel-Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Paris Descartes University, Paris, France

Majd AlGhatrif, MD Human Cardiovascular Studies Unit, Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

Sola Aoun Bahous, MD, PhD Division of Nephrology, Department of Medicine, University Medical Center–Rizk Hospital, Ashrafieh, Beirut, Lebanon

Lucas S. Aparicio, MD, DDS Internal Medicine – Hypertension Section, Hospital Italiano De Buenos Aires, Buenos Aires, Argentina

Annayya R. Aroor, MD, PhD Research Service Harry S Truman Memorial Veterans Hospital, Columbia, MO, USA

Division of Endocrinology and Metabolism, Department of Medicine, University of Missouri School of Medicine, Columbia, MO, USA

Kei Asayama, MD, PhD Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan

Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan

Jeffrey Atkinson, BA, MA, PhD Cardiovascular Pharmacology Laboratory, Pharmacy Faculty, Lorraine University, Nancy University, Nancy, France

Abraham Aviv, MD, PhD Center of Human Development and Aging Rutgers, The State University of New Jersey, New Jersey Medical School, Newark, NJ, USA

Alberto P. Avolio, PhD, BE The Australian School of Advanced Medicine, 2 Technology Place, Macquarie University, North Ryde, Sydney, NSW, Australia

Tine De Backer, MD, PhD Clinical Pharmacology, Heymans Institute of Pharmacology, University Hospital Ghent, Ghent, Belgium

Cardiovascular Diseases, University Hospital Ghent, Ghent, Belgium

Hélène Beaussier Clinical Research Unit and Pharmacy, Fondation Hôpital Saint Joseph, Paris, France

Hopital Europeen Georges Pompidou, Assistance Publique Hôpitaux de Paris, Université Paris Descartes, Paris, France

Jérémy Bellien, PharmD, PhD Department of Pharmacology, Rouen University Hospital, Rouen, France

Athanase Benetos, MD, PhD Department of Geriatrics, University Hospital of Nancy, Universite De Lorraine, Vandoeuvre Les Nancy, France

INSERM U1116, Université de Lorraine, Nancy, France

Yvonnick Bezie, PharmD, PhD Pharmacy Department, Groupe Hospitalier Paris Saint – Joseph, Paris, France

Jacques Blacher, MD, PhD Department of Medicine, Diagnosis and Therapeutics Center, Hôtel-Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Paris Descartes University, Paris, France

José Boggia, MD, PhD Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Montevideo, Uruguay

Luc M. Van Bortel, MD, PhD Clinical Pharmacology, Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

Pierre Boutouyrie, MD, PhD Department of Pharmacology and Institut National de la Santé et de la Recherche Médicale U970(Eq7)-PARCC, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Université Paris-Descartes, Paris, France

Marie Briet, MD, PhD Department of Pharmacology, Centre Hospitalo-Universitaire d'Angers, Université d'Angers, Angers, France

Lady Davis Institute for Medical Research, McGill University, Montreal, QC, Canada

Mark Butlin, PhD, BE The Australian School of Advanced Medicine, 2 Technology Drive, Macquarie University, North Ryde, Sydney, NSW, Australia

Julio A. Chirinos, MD, PhD Philadelphia Veterans Affairs Medical Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

John R. Cockcroft, FRCP, FESC Department of Cardiology, Wales Heart Research Institute, University Hospital, Cardiff University, Cardiff, UK

Julia L. Cook, PhD Research Division, Ochsner Health System, New Orleans, LA, USA

Yazan Daaboul, MSc Department of Medicine, Gilbert and Rose Marie Chagoury School of Medicine, University Medical Center – Rizk Hospital, Ashrafieh, Beirut, Lebanon

Michel Delahousse, MD, PhD Department of Nephrology and Transplantation, Foch Hospital, Suresnes, France

Richard B. Devereux, MD Greenberg Division of Cardiology, New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY, USA

Javier Diez, MD, PhD Program of Cardiovascular Diseases, Centre for Applied Medical Research, Pamplona, Spain

Department of Cardiology and Cardiac Surgery, School of Medicine, University Clinic, University of Navarra, Pamplona, Spain

Feng-Hua Ding, MD, PhD Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Department of Cardiology, Ruijin Hospital, Shanghai Jiatong University School of Medicine, Shanghai, China

Isabel Ferreira, PhD Department of Internal Medicine, Maastricht University Medical Centre, Maasricht, The Netherlands

Stanley S. Franklin, MD, FACO, FAHA, FASN Preventive Cardiology Program, Division of Cardiology, Department of Medicine, C240 Medical Sciences, University of California, Irvine, CA, USA

Edward D. Frohlich, MD, MACP, FACC Department of Cardiology, Ochsner Clinic Foundation, New Orleans, LA, USA

Sylvie Gautier, MD Department of Geriatrics, University Hospital of Nancy, Universite De Lorraine, Vandoeuvre Les Nancy, France

Yumei Gu, MD, PhD Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

Tine W. Hansen, MD, PhD Department of Complications, Steno Diabetes Center, Gentofte, Denmark

David G. Harrison, MD Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University, Nashville, TN, USA

Scott L. Hummel, MD, MS Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Piotr Jankowski, MD, PhD I Department of Cardiology and Hypertension, Institute of Cardiology, Jagielloninan University Medical College, Krakow, Poland

Guanghong Jia, PhD Research Service Harry S Truman Memorial Veterans Hospital,Columbia, MO, USA

Division of Endocrinology and Metabolism, Department of Medicine, University of Missouri School of Medicine, Columbia, MO, USA

Xiongjing J. Jiang, MD Department of Cardiology, Hypertension Centre, Fuwai Hospital, Cardiovascular Institute, Chinese Academy of Medical Sciences, National Centre for Cardiovascular Diseases, Peking Union Medical College, Beijing, China

Robinson Joannidès, MD, PhD Department of Pharmacology, INSERM U1096 Institute for Research and Innovation in Biomedicine, Rouen, France

Bronwyn A. Kingwell, PhD Metabolic and Vascular Physiology, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Serge Korjian, MSc Department of Medicine, Gilbert and Rose Marie Chagoury School of Medicine, University Medical Center – Rizk Hospital, Ashafieh, Beirut, Lebanon

Roel J.J. van de Laar, MD, PhD Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

Patrick Lacolley Faculte de Medecine, Unité INSERM UL U1116, Vandoeuvre Les Nancy, France

INSERM U1116, Université de Lorraine, Nancy, France

Edward G. Lakatta, MD Laboratory of Cardiovascular Science, Biomedical Research Center, Baltimore, MD, USA

Laboratory of Cardiovascular Science, IRP, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

Stéphane Laurent, MD, PhD Department of Pharmacology and Institut National de la Santé et de la Recherche Médicale U970(Eq7)-PARCC, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Université Paris-Descartes, Paris, France

Stephanie Lehoux, PhD Department of Medicine, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, Canada

Bernard I. Lévy, MD, PhD Cardiovascular Research Center- Inserm UMRS 970, Paris, France

Blood and Vessel Institute, Paris, France

Yan Li, MD, PhD Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Li-Hua Li, MD Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Yanping Liu, MD, PhD Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

Gérard London, MD Department of Nephrology, Hopital Manhes, Fleury-Mérogis, France

Laurent Macron, MD, PhD Radiology, HEGP, APHP, Inserm U970 Eq7, Université Paris Descartes, Paris, France

RadiologyHopital Europeen Georges Pompidou, Paris, France

Kaisa M. Mäki-Petäjä, PhD, BSc Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

Yoshio Matsui, MD, PhD Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan

Department of Internal Medicine, Iwakuni Medical Center, Iwakuni, Yamaguchi, Japan

Carmel M. McEniery, PhD Clinical Pharmacology Unit, University of Cambridge, Addensbrooke's Hospital, Cambridge, UK

Gerald A. Meininger, PhD Dalton Cardiovascular Research Center, University of Missouri School of Medicine, Columbia, MO, USA

Department of Medical Pharmacology and Physiology, University of Missouri School of Medicine, Columbia, MO, USA

Jean-Jacques Mourad, MD, PhD Department of Internal Medicine and Arterial Hypertension, Avicenne University Hospital – APHP, Bobigny, France

Elie Mousseaux, MD, PhD Radiology, HEGP, APHP, Inserm U970 Eq7, Université Paris Descartes, Paris, France

RadiologyHopital Euopeen Georges Pompidou, Paris, France

Teemu J. Niiranen, MD, PhD Department of Chronic Disease Prevention, National Institute for Health and Welfare, Turku, Finland

Department of Medicine, Turku University Hospital, Turku, Finland

Caroline O'Brien, PhD Harvard-MIT Biomedical Engineering Center, Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA

Michael F. O'Rourke, MD, DSc Department of Cardiovascular and Hypertension, St. Vincent's Clinic, University of New South Wales, Victor Chang Cardiac Research Institute, Darlinghurst, Sydney, NSW, Australia

Augustine Nonso Odili, MD Department of Internal Medicine, Faculty of Clinical Sciences, College of Health Sciences, University of Abuja, University of Abuja Teaching Hospital, Abuja, Nigeria

Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, Studies Coordinating Centre, University of Leuven, Leuven, Belgium

Bruno Pannier, MD Service de Medecine Interne-Cardiologie, Centre Hospitalier F.H. Manhes, Fleury Merogis, France

Gianfranco Parati, MD Department of Health Sciences, University of Milano- Bicocca, Milan, Italy

Marc A. Pfeffer, MD, PhD Division of Cardiovascular, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Gerard E. Plante Institut de Pharmacologie, Universitye de Sherbrooke, Sherbrooke, QC, Canada

Athanase D. Protogerou, MD, PhD Cardiovascular Research Laboratory and Hypertension Center, First Department of Propedeutic and Internal Medicine, "Laiko" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Francesco Mattace Raso, MD, PhD Department of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Richard N. Re, MD Research Division, Ochsner Health System, New Orleans, LA, USA

Véronique Regnault Department of Geriatrics, Université De Lorraine, Vandoeuvre Les Nancy, France

Unité INSERM, U1116, Vandoeuvre Les Nancy, France

Mary J. Roman, MD Greenberg Division of Cardiology, New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY, USA

Julian W. Sacre, BScApp, PhD Metabolic and Vascular Physiology, Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Michel E. Safar, MD Department of Medicine, Diagnosis and Therapeutics Center, Hôtel-Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Paris Descartes University, Paris, France

Paolo Salvi, MD, PhD Department of Cardiology, S. Luca Hospital, IRCCS Istituto Auxologico Italiano, Milano, Italy

Department of Geriatrics, University Hospital of Nancy, Universite De Lorraine, Vandoeuvre Les Nancy, France

INSERM U1116, Université de Lorraine, Nancy, France

Ernesto L. Schiffrin, MD, PhD Department of Medicine, Lady Davis Institute for Medical Research, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, QC, Canada

Angelo Scuteri, MD, PhD School of Geriatrics – Faculty of Medicine, University of Rome Tor Vergata, Rome, Italy

Patrick Segers, PhD Institute Biomedical Technology (IBiTech), iMinds Medical IT, Ghent University, Campus Heymans- Blok B, Ghent, Belgium

Jean-Sébastien Silvestre, PhD Cardiovascular Research Center- Inserm UMRS 970, Paris, France

Harold Smulyan, MD Cardiology Division, Department of Medicine, Upstate Medical University, Syracuse, NY, USA

James R. Sowers, MD Division of Endocrinology and Metabolism, Department of Medicine, University of Missouri School of Medicine, Columbia, MO, USA

Research Service Harry S Truman Memorial Veterans Hospital, Columbia, MO, USA

Department of Medical Pharmacology and Physiology, University of Missouri School of Medicine, Columbia, MO, USA

Dalton Cardiovascular Research Center, University of Missouri School of Medicine, Columbia, MO, USA

Jan A. Staessen, MD, PhD Department of Cardiovascular Sciences, UZ Leuven Campus Sint Rafael, University of Leuven, Leuven, Belgium

Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

Research Unit Hypertension and Cardiovascular Epidemiology, Department of Cardiovascular Sciences, Studies Coordinating Centre, University of Leuven, Leuven, Belgium

Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, Studies Coordinating Centre, University of Leuven, Leuven, Belgium

Christodoulos Stefanadis, MD, PhD Hypertension and Peripheral Vessels Units, 1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Coen D.A. Stehouwer, MD, PhD Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

Jonathan Stone, BSc (Med), PhD, DSc Department of Physiology, Bosch Institute, University of Sydney F 13, Sydney, NSW, Australia

Harry A.J. Struijker-Boudier, PhD Department of Pharmacology, CARIM, Maastricht University, Maastricht, The Netherlands

Kenji Takazawa, MD, PhD Department of Cardiology, Hachioji Medical Center, Tokyo Medical University, Hachioji City, Tokyo, Japan

Isabella Tan, BE The Australian School of Advanced Medicine, 2 Technology Drive, Macquarie University, North Ryde, Sydney, NSW, Australia

Alain Tedgui, PhD Institut National de la Santé et de la Recherche Médicale (Inserm), Unité 970, Paris Cardiovascular Research Center, Université Paris-Descartes, Paris, France

Dimitrios Terentes-Printzios, MD Hypertension and Peripheral Vessels Units, 1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Lutgarde Thijs, MSc Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

Simon N. Thornton, PhD Faculté de Médecine, Unité INSERM UL U1116, Nancy, France

Christian Thuillez, MD, PhD Department of Pharmacology, INSERM U1096, Institute for Research and Innovation in Biomedicine, Rouen, France

Charalambos Vlachopoulos, MD, PhD Hypertension and Peripheral Vessels Units, 1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Ji-Guang Wang, MD, PhD Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypetension, Ruijin Hospital, Shanghai Jiaotong, University School of Medicine, Shanghai, China

Ghassan Watfa, MD, PhD Department of Geriatrics, University Hospital Of Nancy, Universite De Lorraine, Vandoeuvre Les Nancy, France

INSERM U1116, Université de Lorraine, Nancy, France

Thomas Weber, MD Department of Cardiology, Kinikum Wels-Grieskirchen, Wels, Austria

Paracelsus Medical University, Salzburg, Austria

Ian B. Wilkinson, FRCP, DM, BM BCh Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

Jing Wu Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA

Alexandra Yannoutsos, MD Diagnosis and Therapeutics Center, Hôtel-Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Paris Descartes University, Paris, France

Yi Zhang, MD, PhD Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

Introduction

Three colleagues whose background in medicine arose from their similar interests in cardiovascular research, although they never worked at the same institution, conceived the concept of this textbook. Further, even more unique, they lived throughout their professional careers in three disparate continents and countries: France, Australia, and the United States. Each of them conducted their clinical investigation in cardiovascular medicine. Initially, Professors Safar and Frohlich were interested primarily in a developing area concerned with the hemodynamics of hypertension. They first met in 1962 when Ed Frohlich was on staff of the Research Division of the Cleveland Clinic in Ohio. Michel Safar visited the Cleveland group at that time to exchange thoughts on a now-forgotten topic concerning the underlying mechanisms of "labile" hypertension. Michel was on the Faculty of Medicine at the Broussais Hospital in Paris. They both shared similar thinking about one aspect in the pathogenesis of hypertensive disease: an initial increased cardiac output, which was produced by total body venoconstriction resulting in increased venous return associated with an "inappropriately normal" total peripheral resistance. Ed continued his work with the role of the heart in hypertension and the underlying mechanisms which may explain its increased risk for morbidity and mortality associated with left ventricular hypertrophy. This, of course, stimulated further interest in left ventricular hypertrophy and its interaction with antihypertensive therapy and its impact on cardiac risk. Other factors confounded that risk including the effects of long-term dietary sodium excess on the cardiovascular and renal inter-relationships. Thus, Michel and Ed continued to remain closely related personally and academically in their clinical investigative interests.

During these years, Michel Safar focused his efforts on the pathophysiological mechanisms responsible for the role of the large arteries in hypertension and its consequences in patients with essential hypertension. He and his team of investigators made their major impact on the development of a new area of clinical research responsible for the increasing interest in systolic hypertension in the elderly and the field of "stiffness" of the large arteries. This, of course, brought Michel Safar into the third relationship with Michael O'Rourke whose fundamental research on large arteries in Australia involved work with a physiological pioneer, Michael Taylor, on comparative physiology and computer modeling of arterial networks. This led to clinical studies on ventricular/vascular interactions, intra-aortic balloon counterpulsation, cardiac transplantation and mechanical heart assist devices. His

studies promoted interests in the aging process, which develops slowly from early adulthood and involves stiffening and dilation of the aortic wall. These hemodynamic interests led to the collaborative efforts of Michael and Michel in the fields of pulsatile arterial parameters and aortic rigidity. They now consider the possibility that small vessel disease in the brain, causing dementia, is another consequence of aortic stiffening and early wave reflection, which may be prevented or delayed by measures which reduce effects of aortic stiffening. The immediate result of their relationship was Michel's establishment of a regular series of international workshops in Paris on this new area of research resulting in a remarkably increased pursuit of scholarly activity in both the fundamental and clinical investigative aspects in this area.

Contemporaneously, during these years, Ed Frohlich assumed editorial responsibility for the American Heart Association's journal *Hypertension*, and was delighted to join "forces" with Michel and Michael to publish the periodic proceedings of the workshop in that journal. This is the story of our personal collaborations and continuing research, based on long-standing friendship and the influence of Michel Safar in the three of us joining together our mutual interest. This now has resulted in publication of this volume involving similarly committed colleagues from the world-wide academic community. Indeed, it explains our joint conception of the title and content of this work of long-standing friends and academic co-workers and the large co-authorship of its contributors.

Basic Concepts of the Book

Our most common and classical knowledge on blood pressure and hypertension has been primarily influenced by three key-points. First, the hemodynamic mechanisms of hypertension have been primarily associated with an increase in total peripheral resistance, pointing to a major contribution of the role of small arteries. Second, the respective contributions of the heart, vessels, and kidneys involve major interactions affecting particularly the renin-angiotensin-aldosterone system. Finally, drug treatment modifies substantially cardiovascular morbidity and mortality through the dominant role of blood pressure reduction.

The development of hypertension has considerably matured over the years for two reasons. Firstly, hypertension was no longer considered as a single homogeneous disease, but rather as a mosaic of interacting mechanisms associated with many other interrelated cardiovascular risk factors. Secondly, the primary objectives of study were no longer limited to a discussion of only control of arterial pressure. Primary objectives were focused on the means to diminish the underlying risk of cardiovascular stiffness and its consequences on morbidity and mortality. This goal was considered and pursued through numerous therapeutic trials designed to intervene on those pathophysiological mechanisms and the interrelationships that are involved with the development of injury and disease outcomes of these target organs.

Parts I and II of this book are related to blood pressure involving two different and complementary aspects: the role of arterial wall mechanics and

the underlying mechanisms of risk involving left ventricular hypertrophy and the role of dietary salt excess on the development of cardiac and renal failure through structural and functional impairment.

In Part I, the role of blood pressure in hypertension and cardiovascular diseases was no longer limited to the role of brachial artery BP measurements, frequently explored in the past but extended to the overall remaining portions of circulation, mainly located at the origin of the aorta. Thus, the concept of central blood pressure was introduced for those organs most related to the presence of cardiovascular risk (i.e., the heart, the brain and kidneys). Pressure measurements were associated to evaluations of flow, impedance to pulsatile flow, arterial stiffness, and other critical parameters as pulse amplification. An important aspect of Part I was the difference noted between steady and pulsatile arterial hemodynamics, two parameters highly and differently related to cardiovascular risk. As noted by Michael O'Rourke, most of these parameters refer to the approach suggested in the past by the principal pioneers of pulsatile arterial hemodynamics, McDonald, Womersley and Taylor. One important aspect is the concept of heart-vessel coupling and its consequences on cardiac structure and function.

Part II refers to the relation between blood pressure, the heart and kidneys. The role of vasoactive interactions are not primarily focused in this discussion but involve primarily the role of the underlying mechanisms of risk in left ventricular hypertrophy, heart failure, oxidative stress and nitric oxide, in relation with mainly dietary salt excess in the heart and kidney. Also investigated are details of the value of multicenter trials of pharmacological therapy on cardiovascular and renal function in hypertension and heart failure.

As a consequence, Part III summarizes the principal findings characterizing hypertension and cardiovascular diseases and the disturbed arterial wall mechanics and sodium balance within the cardiovascular system. Such modifications are studied successively in terms of brachial and central BP measurements and take into account both steady and pulsatile arterial hemodynamics, particularly the role of heart rate and pulse pressure amplification. In addition, organ damages are described extensively in Part III, evaluating the particular and specific roles of the heart, the brain and the kidneys.

Parts IV and V are focused on the different aspects of the clinical involvement necessary for evaluation of the cardiovascular system. First, the role of age, sex, metabolic and inflammatory factors is considered in detail. Second, a description of risk stratification is given, primarily affecting arterial stiffness and pulse pressure. The major role of ethnicity is particularly taken into account. Finally, among the various cardiovascular medications associated to treatment, the antihypertensive agents are mainly (but not exclusively) taken into account, studying in particular their impact on arterial stiffness and wave reflections. Each of these considerations are presented in terms of large vessels, based on the privilege of knowledge and not necessarily the evidence of recommendations frequently difficult to demonstrate.

Finally, this book has developed new conceptual approaches of hypertension and cardiovascular risk, taking into account three major points. First, hypertension should involve in its definition not only vascular resistance but also arterial stiffness, wave reflections and vascular rarefaction. Second,

hypertension does not reflect a simple linear relationship between blood pressure and target organ damage but is more complex – and not necessarily linearly affecting mechanical factors and different complications individually associated with the heart, brain and kidneys. Finally, the aim of treatment is no longer limited to a decrease in blood pressure but, rather, a reduction of cardiovascular risk and, in the long term, of residual risk. In this context, it is important that, whereas increased stiffness and early wave reflections caused by aging magnify cardiovascular risk (studies in Part I), the improvement of cardiac function by drug treatment (studies in Part II) may actually exacerbate the adverse effect of increased stiffness and wave reflections when these arterial parameters remain untreated, thereby further increasing cardiovascular risk. Again, it is evident that treatment must verify in the long term the major role of heart-vessel coupling. Modern concepts must include arterial properties as well as peripheral resistance and cardiac function.

Content of the Book

This book is published at the peak of a special evolution during which new concepts and knowledge on blood pressure and cardiovascular risk have been developed over recent years, which is associated with continued exciting aspects of disease and its treatment. First, studies have recognized that the duration of life has increased considerably in recent years promoting research into novel aspects of therapeutic interventions. Second, current investigations on the interactions between genetics and environment still remain difficult to delineate clearly in our patients. These difficulties explain the necessity to obtain numerous contributors participating in all five sections of this volume. Each section is composed of several chapters, each detailed by their respective authors. Importantly, their specific contributions and responsibility, and reflecting any changes by the co-editors. Due to the complexity of the subject, repetitions within this book have not been completely excluded from the studied description by the authors, other than in editorial context to facilitate reading.

Michel E. Safar — Paris, France
Michael F. O'Rourke — Sydney, NSW, Australia
Edward D. Frohlich — Orleans, LA, USA

Part I

Blood Pressure: Basic Concepts of Steady and Pulsatile Arterial Hemodynamics

1 Arterial Stiffness, Wave Reflection, Wave Amplification: Basic Concepts, Principles of Measurement and Analysis in Humans

Michael F. O'Rourke, Caroline O'Brien, and Thomas Weber

Abstract

The arterial system has two functions – as a conduit to deliver blood at high pressure to the organs and tissues of the body according to need, and as a cushion, to reduce pulsations generated by the intermittently-pumping left ventricle, so that blood flow through peripheral high and low resistance vascular beds is steady with little residual pulsation (O'Rourke, Chapter 1: Principles and definitions of arterial stiffness, wave reflections and pulse pressure amplification. In: Safar ME, O'Rourke MF (eds) Arterial stiffness in hypertension. Handbook of hypertension, vol 23. Elsevier, Amsterdam, 2006; Nichols et al., McDonald's blood flow in arteries, 6th edn. Arnold Hodder, London, 2011). The arterial system in man is beautifully suited to serve these functions, at least through childhood, adolescence and young adulthood (Taylor, Gastroenterology 52:358–363, 1967). By mid-life, effects of pulsatile strain on non-living elastic fibres in the highly pulsatile aorta lead to their fracture and to progressive passive aortic dilation, with transfer of stress to more rigid collagen fibres in the media (Nichols et al., McDonald's blood flow in arteries, 6th edn. Arnold Hodder, London, 2011). Such changes have adverse effects on arterial function and ideal timing of vascular/ventricular interaction (O'Rourke and Nichols, Hypertension 45:652–658, 2005; Laurent et al., Eur Heart J 27:2588–2605, 2006; O'Rourke and Hashimoto, J Am

M.F. O'Rourke, MD, DSc (✉)
Department of Cardiovascular and Hypertension,
St Vincent's Clinic, University of New South Wales,
Victor Chang Cardiac Research Institute,
Suite 810 St Vincent Clinic, 438 Victoria Street,
Darlinghurst, Sydney, NSW 2010, Australia
e-mail: m.orourke@unsw.edu.au

C. O'Brien, PhD
Harvard-MIT Biomedical Engineering Center,
Institute for Medical Engineering and Science,
Massachusetts Institute of Technology,
77 Massachusetts Ave, Cambridge, MA 02139, USA
e-mail: ccob@mit.edu

T. Weber, MD
Department of Cardiology, Klinikum Wels-Grieskirchen,
Grieskirchnerstrasse 42, Wels 4600, Austria

Paracelsus Medical University, Salzburg, Austria
e-mail: thomas.weber3@liwest.at

M.E. Safar et al. (eds.), *Blood Pressure and Arterial Wall Mechanics in Cardiovascular Diseases*,
DOI 10.1007/978-1-4471-5198-2_1,

Coll Cardiol 50:1–13, 2007). As later years pass, impaired arterial function plays an important role in morbidity and mortality, becoming a key factor in development of Isolated Systolic Hypertension of the Elderly (ISHE), and cardiac failure (Chirinos et al. 2012; Weber et al. 2013) and of cerebral micro-infarcts and hemorrhage with cognitive impairment and dementia (O'Rourke and Safar ME, Hypertension 46:200–204, 2005; Stone, Med Hypotheses 71:347–359, 2008; Gorelick, Stroke 42:2672–2713, 2011). This introductory chapter discusses mechanisms and introduces strategies for treatment and prevention.

Keywords
Arterial stiffness • Wave reflection • Pressure amplification • Aging • Pulse wave velocity • Impedance

Concepts

Arterial stiffness and distensibility (Table 1.1) are difficult to measure directly in the human arterial system. Normally up to young adulthood, distensibility is high (stiffness is low) in the proximal thoracic aorta and distensibility is less (stiffness greater) in the abdominal aorta and peripheral arteries [1, 2]. This is the pattern seen in most other mammals throughout life; benefits resulting have been set out by Taylor [3]. Distensibility measured in one arterial segment is not necessarily the same as distensibility at another segment [2]. Further, pressure pulsation is not the same in all arteries and diameter change is small – (2–16 %), and hard to measure accurately [1–6]. The arterial wall is not homogeneous, and stresses are controlled by the medial, not intimal elements. Stiffness and distensibility are not only difficult to measure, but measures are bound to be inaccurate, and they have not always been shown of value in predicting cardiovascular events [1, 5, 8]. However, indirect measures of arterial stiffness have proved useful, and are widely used now to predict cardiovascular events [1, 5]. Such indices are directly (pulse wave velocity [1, 2]), or indirectly, related to arterial stiffness (aortic augmentation index), and amplification of the arterial pressure wave between aorta and radial artery (to be later discussed).

Table 1.1 Indices of arterial stiffness

Elastic modulus	The pressure step required for (theoretic) 100 % stretch from resting diameter at fixed vessel length, $(\Delta P \cdot D) \div \Delta D$ (mmHg)
Arterial distensibility	Relative diameter change for a pressure increment; the inverse of elastic modulus, $\Delta D \div (\Delta P \cdot D)$ ($mmHg^{-1}$)
Arterial compliance	Absolute diameter; change for a given pressure step, $\Delta D \div \Delta P$ ($cm \cdot mmHg^{-1}$)
Volume elastic modulus	Pressure step required for (theoretic) 100 % increase in volume $\Delta P \div (\Delta V \div V)$ (mmHg) $= \Delta P \div (\Delta A \div A)$ (mmHg) (where there is no change in length)
Volume compliance	Absolute volume change for a given pressure step or an arterial segment $\Delta V \div \Delta P$ ($cm^3 \cdot mmHg^{-1}$) or $\Delta A \div \Delta P$ ($cm^2 \cdot mmHg^{-1}$), if there is no change in length
Young's modulus	Elastic modulus per unit area; the pressure step per square centimetre required for (theoretic) 100 % stretch from resting length $(\Delta P \cdot D) \div (\Delta D \cdot h)$ ($mmHg \cdot cm^{-1}$)
Pulse wave velocity	Speed of travel of the pulse along an arterial segment, distance $\div \Delta t$ ($cm \cdot s^{-1}$)
Characteristic impedance	Relationship between pressure change and flow velocity in the absence of wave reflections $(\Delta P \div \Delta V)$ (mmHg. $cm^{-1}.s$)
Stiffness index	Ratio of logarithm (systolic/diastolic pressures) to (relative change in diameter) $\beta = \ln(P_s \div P_d) \div [(D_s - D_d) \div D_d]$ (nondimensional)

Distensibility (and stiffness) are useful and necessary concepts, and had been used in the past to characterise properties of the arterial tree. The whole arterial tree was likened by Stephen Hales (the first to actually measure blood pressure [12]), to the inverted air-filled dome ("Windkessel" in the German translation) of contemporary (circa 1770) hand-pumped fire engines. The problem with this model was its inability to explain pressure wave contour under different physiological or pathophysiological conditions. In such a model, pressure is everywhere the same – there is no wave travel, no wave reflection, no augmentation and no amplification of the pulse in peripheral arteries. Readers will find support for Windkessel models in other chapters of this book, usually by non-clinicians. Clinicians who see a future for analysis of pulse waveforms require comprehensive realistic models for use in situations such as intensive care where a wide range of blood pressure, heart rate, age and disease exist. Here, the model of transmission line is necessary for realistic monitoring, analysis and diagnosis.

The best and the only comprehensive model of the arterial tree is a simple tube (Fig. 1.1) [1, 2], open at one end to receive blood in spurts from the left ventricle, and closed at the other end which represents the sum total of high resistance arterioles in which the elastic arteries terminate. Such a model allows for wave travel along the tube (and back again) after wave reflection at the distal end. In this model, one can see and explain the known properties of the arterial system – delay of the pulse between proximal and distal arteries, difference in shape and amplitude of the pulse in proximal aorta and distal arteries, and wave reflection (Fig. 1.2).

So what is wave reflection? This is best understood by considering the difference between pressure and flow waves in the ascending aorta. The flow wave from the heart shows a single spurt, whereafter flow falls to zero at the incisura, and stays at zero throughout diastole. In contrast, the pressure wave shows two localised peaks, the first corresponding to the peak of flow and the second to the summation of reflection from multiple sites, principally in the trunk and lower body. In children and young adults, the second peak is in diastole, after the incisura caused by aortic valve closure. In older adults, the aorta is stiffened and pulse wave velocity increased, so that the reflected wave returns early from peripheral arterioles, and augments pressure in mid-late systole (Fig. 1.2).

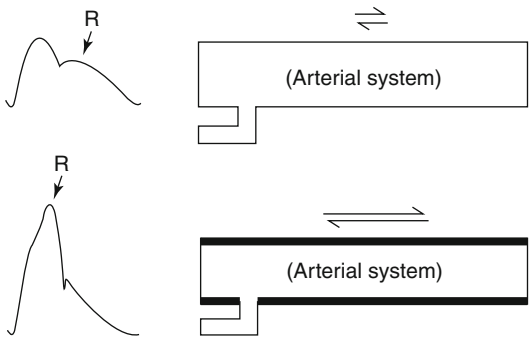

Fig. 1.1 Tubular models of the arterial system with the heart (*left*) and conduit arteries (*right*). Pressure waves in the ascending aorta are shown at *left side*. The normal young arterial tree is represented at *top*, while the old stiffened arterial tree is represented at *bottom*. *Arrows* represent speed of pulse wave travel to the peripheral resistance and back to the heart

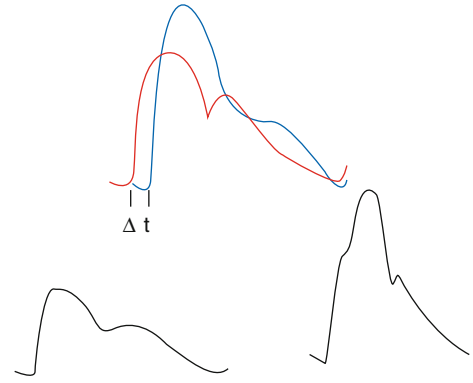

Fig. 1.2 *Top*: The time delay (**Δ**t) due the pressure wave travelling from the ascending aorta (*red*) to the femoral artery (*blue*). The time delay (**Δ**t) is used in the determination of "ascending aortic" pulse wave velocity, where the distance between carotid and femoral arteries is divided by time required for the pressure wave to travel. *Bottom*: Ascending aortic pressure wave in a young individual (*left*) and old subject with stiffened arteries (*right*)

Pulse Wave Velocity: The Best Currently Available Non-invasive Measure of Arterial Stiffness

Pulse wave velocity (PWV) is the speed of the pulse wave generated by the heart, along the arterial tree. It is considerably higher (5–15 M/s) than the blood flow velocity (peak ~1 M/s) and is determined by properties of the arterial wall and of blood within. It is determined by the stiffness of the segments of arterial tree traversed by the pulse according to the Moens-Korteweg equation [1, 2]:

$$PWV = \sqrt{\frac{E/h}{\rho.D}},$$

where "E" is stiffness of the arterial wall as Young's modulus [1], "h" is wall thickness (assuming homogeneity), "ρ" is kinematic viscosity of blood = blood viscosity ÷ density, and "D" is diameter. Typical values of ascending aortic PWV of a child are 3–5 M/s. This can be compared to peak flow velocity in the ascending aorta (~1 M/s) and the height of the human body in a 12 year-old child 1–1.5 M, and distance from heart to resultant peripheral reflecting site of ~0.5 M [1, 2]. A reflected pressure wave would be expected to appear some 300 ms after the foot of the pressure wave and to be most prominent after the aortic valve shuts. In an older adult, with aortic PWV 10 M/s and height 1.5–2 M, the reflected wave would be expected in late systole. Both waves in Fig. 1.2 are typically what one sees in young and old human respectively.

PWV in the aorta can be estimated from measurement of distance from aortic origin to femoral artery, then measuring the delay in the foot of the wave between ascending aorta (or carotid with correction of delay from aorta to carotid site) to femoral artery [13]. Typical values for a young adult are distance 0.6 M, delay 100 ms, and "aortic" PWV of 6 M/s.

Efficiency of the arterial tree, as referred to above, was one of the key interests of pioneers of this field such as Donald McDonald and Michael Taylor, some 50 years ago [2, 3]. It had been alluded to by Hales [12] in 1769 as the cardiovascular "oeconomy". Taylor noted that aortic PWV was always slightly higher than peak flow velocity from the left ventricle (in a child 3 M/s compared to 1 M/s respectively) so there would be no concern about development of shock waves in the aorta, and that there was such correspondence between PWV, body length and heart rate that wave reflection would normally return to the heart after ventricular ejection had ceased, and so would not increase left ventricular load of that beat. On the other hand, the reflected boost to pressure during diastole would maintain coronary perfusion pressure during diastole – the only period when the left ventricular muscle was relaxed and capable of being perfused. Taylor commented on these desirable features of arterial function, showed that they were retained in mammals of different size and responsible for the inverse relationship between body size and heart rate [3]. Milnor [14] and O'Rourke [15] later highlighted these issues, with the latter pointing out how the optimal timing of wave reflection was lost with aging as aortic PWV increased and wave reflection arrived early to augment pressure or suppress flow [1, 2, 6] from the heart in late systole.

Fifty years back [2], the marked increase of aortic PWV with age in humans was not appreciated, nor were the ill-effects this had on the heart. Maximal efficiency of the arterial tree appears to decrease progressively from around age 30. This corresponds to the average life span in earlier times; hence arterial degeneration after age 30 [2, 6] did not pose an evolutionary threat to the human species.

Principles of Measurement, Analysis

Invasive studies of arterial pressure and flow waves were undertaken up till around 1950 by physiologists exclusively, initially by pioneers such as Starling, Frank and Wiggers, then after devastation of Europe by two World Wars and their sequelae, later by luminaries of American Physiology such as Hamilton, Dow and

Remington. Concepts of this time are prominently displayed in the Handbooks of the American Physiological Society [16]. However, physicians of the late nineteenth century (i.e. 60 years before) had sought clinical information through analysing radial and carotid pulse waves as introduced by Marey and Mahomed, using mechanical sensors and smoked drums, but these lapsed with introduction of the cuff sphygmomanometer, and the numbers they provided for brachial cuff systolic and diastolic pressures [17]. Electronic sensors were introduced by Wiggers and Hamilton for measurement of pressure waves, then electromagnetic flow cuffs for direct application to an artery were introduced just prior to World War 2. Physiologists using these devices were generally aware of the shortcomings of the devices they used for measuring pressure and flow, and the potential artefacts that accompanied their use, as well as concerns on frequency response of recording systems. Around this time, and even later, medical device industries were primitive or non-existent, and physiologists needed to make and calibrate their own [18]. As late as 1964, Taylor's laboratory in Sydney made its own cuff electromagnetic flowmeter probes, and callipers for measuring pulsatile diameter change, and calibrated these for steady and pulsatile response. In the process, physiologists became very aware of instrumental and analytic shortcomings [19], but were guided by the traditions of their profession, inherited from European masters including Carl Ludwig that "Die Methode ist Alles" [19].

Shortly after conclusion of World War 2, the field of arterial hemodynamics was taken up again, particularly in the USA with the field of coronary hemodynamics investigated thoroughly by Donald Gregg [20] and colleagues at the Walter Reid Hospital in Washington using cuff electromagnetic flowmeters, then by Braunwald and colleagues [21] at the National Institute of Health for study of animal and human heart function. Enthusiastic development of cardiac surgery and cardiac catheterisation widened the field, introducing more and better instruments, but eventually a degree of laxity on fundamentals – a straying from the dicta of Ludwig. This was later associated with break-up of the American Physiological Society so that Neurophysiology joined Neuroscience, and Cardiovascular Physiology became largely a clinical discipline. Similar changes in allegiance have occurred elsewhere, but for Physiology, incorporation with anatomy or clinical science can be seen as a backward step in medical pre and postgraduate education.

Up until the late 1960s, the strong departments of academic cardiovascular physiology were directed by those who sought to examine cardiovascular physiology in the time domain, as it had been prior to the Second World War [16]. Alternative approaches, developed largely in emerging departments of Biomedical Engineering, were spurred on by physiologists/mathematicians McDonald, Womersley and Taylor in Britain who espoused analysis of pressure and flow in the frequency domain, with pressure wave transmission described in terms of transfer functions of modulus and phase plotted against frequency, and pressure/flow relationships described as modulus and phase of impedance [2, 22, 23]. These analytic principles are now regarded as complementary, but they are often not familiar to the modern conventionally-trained physicians and clinical scientists who now dominate the field of arterial hemodynamics, and are strongly represented in this book.

Modern advances in arterial hemodynamics, as used in clinical departments, were first developed in experimental animals where it was possible to control variables in a way that is not possible in clinical practice. Clinicians work in an environment when advance needs be made in the process of treating patients to the highest possible standards. Corners need be cut and approximations made. Such need is a fact of life, and not necessarily undesirable. Indeed McDonald's new approach was based on the assumption (quantified by Womersley [23]), that non-linearities in pressure/flow relations were sufficiently small to be neglected to a first approximation. However, many problems have arisen in clinical practice with respect to the issues previously discussed in this chapter, and warrant consideration when reading what follows in later chapters.

Wave Reflection

Readers will find considerable confusion on this subject in recent publications [24], and even in this book. The view presented in this chapter is conventional and mainstream – that promoted by Wiggers and other classic physiologists at the time of the peak influence of the American Physiological Society and the (British) Physiological Society [2, 16], and by Taylor and colleagues on the basis of conventional physiology and from analysis of pressure and flow waves in both the time and frequency domain. This view notes studies extending back to Galen and Harvey, implemented by master surgeon John Hunter in 1775 [25] for treatment of popliteal aneurysms. These are interpreted now to show that wave reflection has greatest effect on the low frequency components of flow and pressure waves (i.e. those of greatest magnitude) and least effect on higher harmonics which are highly damped [26]. A different point of view is promoted by groups in Calgary [27] and London [28] who see greatest effect of wave reflection on higher harmonics. The views are based on studies from a single human catheterisation laboratory in London, and are debated sometimes scathingly [29] as reactionary "Cross Talk" in 2013 editions of the Journal of Physiology (London) [27], and in other journal correspondence [29]. Early wave reflection in the ascending aorta, as manifest from pressure wave augmentation, ratio of backward to forward wave or as pressure wave amplification has been shown to predict cardiovascular events in the majority (14/19) of reported studies (Table 1.2). In the five negative studies, amplification was not measured with validated methods.

Another viewpoint on wave reflection is voiced in a series of articles from distinguished authors in the main clinical journal of the American Heart Association where magnitude of wave reflection is gauged from magnitude of aortic augmentation index, without consideration of effects of wave reflection on flow from the heart. Wave reflection can subtract from flow as well as add to pressure [2, 30, 31]. To properly interpret pressure waves in the arterial system one needs to consider not only shape of the pressure wave but the flow wave that generates the pressure wave [2, 9]. This is why the best description of LV hydraulic load is as vascular impedance, and this requires measurement of flow as well as pressure, then describing the relationship in the frequency domain as pioneered by Taylor and Milnor 50 years ago [32, 33].

Another problem in interpretation of impedance and flow waveforms in human studies has been the use of Doppler flowmetry in the left ventricular outflow tract from the envelope of the flow wave and the assumption of laminar flow in the ascending aorta. The envelope of flow represents highest velocities in a turbulent jet and does not represent average flow across the aorta at any point in time. The turbulence can be seen in Magnetic Resonance (MR) studies as forward and backward flow occurring at the same time and as previously mentioned. The MR analysis enables backward and forward flow to be separated, with instantaneous mean flow estimated across the aortic lumen [34, 35]. MR ascending aortic flow shows the predicted pattern, as previously shown in experimental animals and humans with cuff type electromagnetic flowmeters. MR ascending aortic flow (peak and mean) is less than Doppler flow, and decreases with age in line with increase in aortic cross-sectional area. Such differences in flow are not seen in Doppler studies, nor in multiple impedance values reported therefrom [36–38].

Amplification of the Pressure Wave

Amplification of the pressure wave (Fig. 1.3) in the upper limb is expressed as amplitude of radial pulse pressure divided by central aortic pulse pressure. It is independent of brachial cuff pressure since it is a ratio of pressures, and ranges between 0 (in older subjects) and 2 (in younger subjects), and is inversely related to augmentation index, and is caused by wave reflection as this influences the timing of the reflected wave in aorta and radial artery. Wave reflection is known to be high (0.80 estimated by O'Rourke and Taylor in a vascular bed [32, 39, 40] and up to 100 % by Hamilton and others [16]) but cannot

Table 1.2 Wave reflections and risk predictions

Author	Population	n	Method	Endpoint	Independent of	Significant parameter
London	ESRD	180	Carotid PWA	Mortality	DBP	AIx
Takenaka	ESRD	104	Radial PWA	CV events	n/a	AIx
Covic	ESRD	92	Aortic (GTF) PWA	Mortality	bSBP, bPP	–
Verbeke	RTX	512	Aortic (GTF) PWA	CV events	bSBP, MBP, PWV	AP, (AIx)
Weber	CKD 3,4	111	Aortic (GTF) PWA	Cardiorenal events	MBP	AIx, AP
Ueda	Coronary intervent	103	Aortic PWA	Restenosis	n/a	AIx
Weber	Coronary intervent	262	Aortic (GTF) PWA	CV events	bSBP, bPP	AIx
Weber	CAD	520 m	Aortic (GTF) PWA	CV events	MBP, bPP	AIx
Chirinos	CAD	297 m	Aortic PWA	CV events	MBP, bPP	AIx, AP
Weber	CAD	725	Aortic (GTF) PWA, WSA	CV events	MBP, bSBP, DBP	AIx, AP, Pb
Sung	Heart failure hosp	120	Carotid PWA, WSA	CV events	MBP	AP, Pb
Sung	Heart failure hosp	80	Carotid PWA	CV events	n/a	AP
Wang	Community	1,272	Carotid PWA, WSA	CV mortality	MBP, bSBP, bPP, PWV	Pb, (AP)
Mitchell	Community	2,232	Carotid PWA	CV events	bSBP	–
Chirinos	Community	5,960	Radial PWA, WSA	CV events/HF	bSBP, DBP	AIx, RM
Benetos	Very elderly	1,126	Carotid PWA	Mortality	n/a	–
Williams	Hypertensives	2,199	Aortic (GTF) PWA	CV + renal events	n/a	(AP)
Dart	Hypertensives	484 f	Carotid PWA (?)	CV events	n/a	–
Manisty	Hypertensives	259	Carotid PWA	CV events	DBP	–

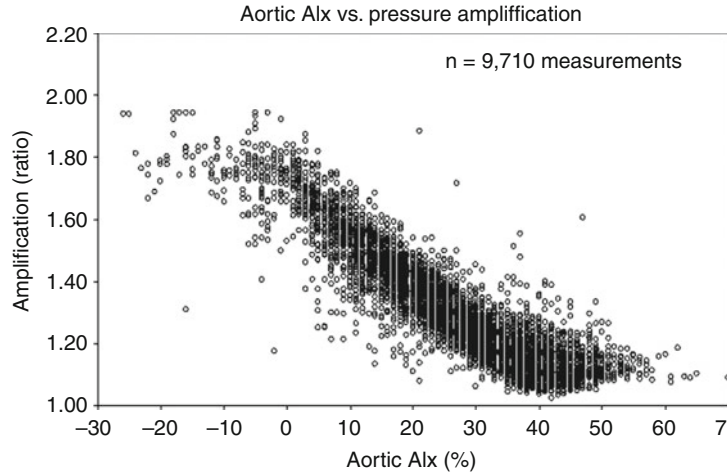

Fig. 1.3 Pulse pressure amplification (brachial pulse pressure/aortic pulse pressure) plotted against aortic augmentation index (AIx) calculated as augmented pressure divided by pulse pressure. There was significant difference in pressure amplification between subjects with aortic AIx more than 0 % and aortic AIx greater than or equal to 50 % ($p<0.0005$). This range contained over 98 % of all data (Reproduced with permission from O'Rourke and Adji [52])

be above unity (or below zero). The greatest value approximating 100 % is seen for positively reflected waves from "closed end" sites where low resistance arteries terminate in high resistance arterioles summate at the periphery (e.g. radial site) [41]. The lowest value approximating zero (Fig. 1.3) is seen when the reflected wave is of similar height in peripheral and central arteries because of high aortic impedance at low frequencies in persons with stiffened arteries [32].

Amplification of the pressure wave in the upper limb as measured invasively or as generated by the SphygmoCor (AtCor) method non-invasively is similar to that measured by the Omron HEM9000 (Omron) non-invasive device, but both are different to amplification described by van Bortel [42] and by Mitchell [43] who base their calibrations on brachial artery tonometry and who find no amplification between brachial and carotid arteries but extreme amplification between the brachial and radial arteries. This anomaly (referred to as the Popeye phenomenon, on the basis of a cartoon character with huge forearms) is not seen in directly recorded pressure waveforms, and is attributable to an inability to applanate (flatten) the anterior surface of the brachial artery when not supported by bone behind, and covered superficially by the rigid brachial aponeurosis [44]. This issue has confused and continues to confuse many clinician scientists, but is explained on the basis of theory and practice of applanation tonometry, and on estimation of amplification from brachial mean and diastolic pressure. The brachial artery wave, measured by tonometry, is blunted at its peak, and shows a Form Factor ((mean pressure – diastolic pressure) ÷ pulse pressure) identical to carotid and aortic pressure. Since amplification is determined by the ratio of Form Factors between the sites, calculated carotid and central pulse pressures appear identical [44].

While wave reflection from the lower body has substantial effect on the ascending aortic pressure wave (as a consequence of more reflecting sites in the lower than upper body), wave reflection in the upper limb has little or no effect on the ascending aortic pressure wave in humans [45]. Amplification in the upper limb is however, of substantial clinical significance since arterial pressure is conventionally measured by cuff sphygmomanometer at the brachial site (providing just peak and nadir of the wave) or when more accuracy or detail is desired, in the radial artery by a catheter or cannula. The principles enunciated above can best be applied to the cardiovascular system by generating the aortic pressure wave from the radial pressure pulse. This can be done by using the transfer function, applied to the radial artery pulse, measured non-invasively by applanation tonometry and calibrated to brachial cuff peak and trough pressures, or from the radial artery pulse recorded directly by invasive cannulation [2]. It is appropriate to use the transfer function technique because the transfer function for pressure wave transmission in the upper limb is applicable in all fully grown