Adel Berbari
Giuseppe Mancia
Editors

Arterial Disorders

Definition, Clinical Manifestations, Mechanisms and Therapeutic Approaches

Springer

Arterial Disorders

Adel Berbari • Giuseppe Mancia
Editors

Arterial Disorders

Definition, Clinical Manifestations, Mechanisms and Therapeutic Approaches

Springer

Editors
Adel Berbari
American University of Beirut
Medical Center
Beirut
Lebanon

Giuseppe Mancia
University of Milano Bicocca IRCCS
Istituto Auxologico Italiano
Milan
Italy

ISBN 978-3-319-14555-6 ISBN 978-3-319-14556-3 (eBook)
DOI 10.1007/978-3-319-14556-3

Library of Congress Control Number: 2015935349

Springer Cham Heidelberg New York Dordrecht London
© Springer International Publishing Switzerland 2015
This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

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

Preface

Cardiovascular disorders account for the increased morbidity and mortality that accompanies a large number of diseases, including diabetes mellitus, obesity, hypertension, nephropathies and rheumatoid arthritis. Recent progress in knowledge has led to an increased understanding of the pathophysiologic mechanisms that underlie vascular alterations in these diseases, the evidence being that a wide range of factors are likely to participate to a variable degree in each of them. Aim of this book is to describe the physiology of macro- and microcirculation together with their interactions. It is also to discuss the structural and functional alterations that macro- and microcirculation develop with diseases, with attention to their hemodynamic, metabolic, humoral, hormonal, inflammatory, as well as genetic or environmental nature. Emphasis is placed on recent notions, such as the involvement of arterial stiffness in the initiation and progression of atherosclerosis, as well as in the age-related alterations of systemic and renal vasculature; the importance of mineral-bone-vascular interactions; the diagnostic and prognostic significance of new noninvasive measures of vascular structure and function in the retina and the kidney; the role of toxemia in pregnancy; and the modern perception of diabetes as a vascular disease. Some chapters are also devoted to the anatomy and the factors involved in atherosclerosis, arteriosclerosis and remodeling of precapillary resistance vessels, and to the vascular changes and interactions with respiratory processes in pulmonary hypertension. Evaluation procedures as well as the full range of available therapeutic options, including lifestyle modifications and pharmacologic approaches, are described and appraised. We hope that clinicians with a specific interest in arterial diseases, but also those operating in other areas of medicine, will find this comprehensive update useful and timely.

Beirut, Lebanon — Adel E. Berbari
Milan, Italy — Giuseppe Mancia

Contents

Part I

Introductory Aspects

Definition and Epidemiology of Arterial Disease

1

Reza Aghamohammadzadeh, Danielle Ormandy, and Anthony M. Heagerty

1.1 Introduction

Cardiovascular diseases (CVDs) are the number one cause of death globally and account for around a third of all deaths worldwide [1, 2]. In 2008, an estimated 17.3 million people died from these conditions which is 48 % of noncommunicable diseases; of these, 6.2 million were a consequence of stroke and 7.3 million due to coronary artery disease [3]. In the UK alone, 160,000 people died of CVD in 2001 [4]. The number of deaths from CVDs is predicted to rise to around 23 million by 2030 [5], thus highlighting the need for better understanding of these disorders and exploration of new treatment and prevention strategies both at individual and population level. Developing countries will suffer a similar fate if steps are not taken urgently.

As the name suggests, cardiovascular diseases are a consequence of pathobiological processes afflicting the heart and blood vessels. A number of disorders pertaining to the heart are also vascular in origin; these include coronary artery disease and microvascular disease within the myocardium. Arterial disorders can be split into coronary, cerebrovascular and peripheral disorders based on the vascular bed, but from a pathological perspective, the underlying processes can be grouped into five categories: atherosclerosis, arterial stiffness, endothelial dysfunction, neurohormonal

R. Aghamohammadzadeh (✉) • A.M. Heagerty
Institute of Cardiovascular Sciences, University of Manchester,
46 Grafton Street, Manchester M13 9NT, UK
e-mail: Reza.zadeh@manchester.ac.uk; Tony.heagerty@manchester.ac.uk

D. Ormandy
Institute of Cardiovascular Sciences, Central Manchester University Hospitals NHS Foundation Trust (Manchester Royal Infirmary), Oxford Road, Manchester M13 9WL, UK
e-mail: Danielle.ormandy@doctors.org.uk

© Springer International Publishing Switzerland 2015

A. Berbari, G. Mancia (eds.), *Arterial Disorders: Definition, Clinical Manifestations, Mechanisms and Therapeutic Approaches*,
DOI 10.1007/978-3-319-14556-3_1

interactions and vascular remodelling. These processes often coexist in a range of disorders including diabetes mellitus, hypertension, obesity and chronic kidney disease.

1.2 Pathophysiology

Cardiovascular disorders are a heterogeneous group of diseases which share common underlying pathological manifestations. Atherosclerosis is a complex phenomenon and itself a result of a combination of pathological processes including inflammation and endothelial damage. Far from a simplistic view that atherosclerosis is lipid driven and predominantly a cholesterol-related disorder, more recently a number of inflammatory cells have been implicated in the process including monocytes [6], macrophages [7], neutrophils [8] and dendritic cells [9], and further exploration of novel chemokines including CCL2 [10], CCL17 and macrophage migration inhibitory factor [10] can yet advance our understanding of the disorder. A better understanding of the role of inflammation in atherosclerosis can in theory lead to the introduction of immunomodulators alongside statins to treat those with difficult-to-control atherogenic dyslipidaemia.

Endothelial dysfunction is characterised by processes which result in attenuated endothelial vasodilatation, either by reducing the bioavailability of nitric oxide or by increasing levels of endothelium-derived vasoconstrictor and prothrombotic factors [11]. Endothelial dysfunction has been described in diabetes mellitus [12–14], hypertension [15, 16], aging [17–19], chronic kidney disease [20] and obesity [21, 22] and contributes to formation of atherosclerotic plaques and vascular stiffness.

Vascular remodelling is an adaptive process in response to long-term changes in the haemodynamic environment that ultimately may contribute to vascular and circulatory disorders. Four main processes have been implicated in remodelling: cell growth, cell death, cell migration and extracellular matrix production or degradation [23]. The specific type of remodelling depends on the disease process necessitating the change within the vasculature. Eutrophic remodelling (rearrangement of the same cellular material around a narrowed lumen resulting in increased media/lumen ratio) has been described in patients with essential hypertension [24] and hypertrophic remodelling (increase in wall thickness or media cross-sectional area and preservation of the lumen diameter) in individuals with diabetes [25–27]. Similarly, obese patients exhibit an increase in media-to-lumen ratio in keeping with hypertrophic remodelling [28], and persistent weight loss following weight-loss surgery regresses these vascular changes [29].

Over the past 10 years, microRNAs have emerged as a rapidly advancing domain offering much promise to enhance our understanding of the pathobiology of CVDs at the molecular and cellular level. MicroRNAs are small noncoding RNAs involved in post-transcriptional gene regulation by binding to mRNA sequences resulting in a reduction of protein expression or leading to mRNA degradation [30]. The potential involvement of microRNAs has been reported in atherosclerosis [31, 32], endothelial cell function [30] and arterial remodelling [33], as well as in disorders such

as peripheral arterial disease [34], stroke [35], obesity [36] and aortic disease [37]. A better understanding of the role of microRNAs in cardiovascular disorders will no doubt lead to development of future therapies [38].

1.3 Investigating Arterial Disorders

Over the years, a variety of techniques have been utilised to study the micro- and macro-circulation at molecular, cellular and tissue level. These include functional assessments of vessel wall and luminal changes using wire and pressure myography, arterial stiffness studies using pulse wave velocity measurements as well as high-resolution ultrasound assessment of endothelial function using flow-mediated dilatation, evaluation of reactive hyperaemia using gauge-strain plethysmography and more recently, pulse amplitude tonometry [39, 40]. One of the most recent developments in the field of cardiovascular investigations is the emergence of retinal artery imaging as a means of assessment and monitoring of arterial disease. The retinal microcirculation offers a noninvasive and easily accessible window to the human microvasculature. Advances in imaging technology using computer-based analysis of retinal photographs allow for reproducible means for quantification of retinal vascular calibre. Changes in retinal vascular calibre are associated with age, ethnicity and genetic factors [41]. Changes such as narrowing of retinal arteriolar calibre, enhanced arteriolar wall reflex and wider venular calibre are associated with the metabolic syndrome [42, 43], waist circumference [44, 45], higher triglyceride levels [45], diabetes and hypertension [44, 46] as well as stroke [47, 48], coronary microvascular disease [49] and coronary artery disease [50]. Retinal microvascular changes can predict subsequent vascular events following ischaemic stroke [51]. These changes are also observed in the paediatric and adolescent population [52–54]. Retinal microvascular signs such as venular dilatation are associated with CKD both in the presence and absence of diabetes, thus reinforcing the link between renal and retinal microvasculature independently of diabetes [55].

1.4 Risk Factors

Identifying major risk factors for arterial disorders with the aim of developing new therapies and public health strategies to reduce cardiovascular mortality and morbidity has been at the forefront of efforts by major healthcare, academic, pharmaceutical and governmental bodies. However, despite our best efforts, cardiovascular diseases are on the rise, and controlling and treating their risk factors remain a major challenge.

Obesity has emerged as a major global healthcare burden and a symptom of our unhealthy lifestyles. In the most simplistic terms, obesity is a result of the imbalance between calories consumed versus calories expended. The worldwide prevalence of obesity has nearly doubled between 1998 and 2008. Over half a billion adults over 20 were obese in 2008 (10 % of all men and 14 % of all women) [56]. The obesity

prevalence tripled from 7 % in lower-middle-income countries to 24 % in upper-middle-income countries. In low- and medium-income countries, there is a positive correlation between socioeconomic status and obesity; however, in the European Union, there seems to be an inverse relationship between education and obesity/BMI [57–60]. These trends most likely reflect the growing awareness of the detrimental effects of obesity on health in the developed countries which should extend to the developing countries in the not-too-distant future and help reduce the mortality rate from 2.8 million deaths each year (2008) as a result of overweight and obesity [1]. In the context of the metabolic syndrome, obesity often coexists with hypertension, diabetes and high cholesterol. There is an intricate interplay between the components of the metabolic syndrome which is evident from both cellular and epidemiological data. For example, those with a raised waist circumference are twice as likely to have high blood pressure [61]. The interplay between adipose tissue and adjacent vasculature has been studied in the context of perivascular adipose tissue and adipokines with vasoactive properties. White adipocytes are the main constituents of perivascular adipose tissue (PVAT) which surrounds a large proportion of blood vessels in the human body and secretes molecules known as adipokines. Healthy PVAT exerts a vasorelaxant effect mediated via a number of potential candidates including adiponectin [62], nitric oxide [63], hydrogen sulphide [64] and methyl palmitate [65]. In obesity, the vasorelaxant effect is not observed thus, in theory, contributing to increased resting tone in peripheral small arteries. Interestingly, weight loss following bariatric (weight loss) surgery restores the PVAT vasorelaxant effect with its potential beneficial effects on resting BP [66]. These recent data are encouraging as they indicate the potential for reversal of a degree of the obesity-induced cardiovascular damage.

Smoking is thought to cause around 10 % of cardiovascular diseases worldwide [1]. Globally, there are more than one billion smokers, and despite a decrease in the use of tobacco products in high-income countries, the total number of smokers is increasing given that 80 % of the world's smokers live in low- and middle-income countries. Smoking kills 5.4 million people a year and has resulted in 100 million deaths in the twentieth century [67]. Smoking cessation is very effective at reducing mortality, and in those with coronary heart disease, it leads to a 36 % reduction in crude relative risk of mortality [68]. The recent emergence and popularity of E-cigarettes has proven controversial given that they may be a helpful aid to smoking cessation, but the hype around the new products might lead to a renewed interest in nicotine-based products and in some cases serve as an introduction to cigarette smoking. The true effect of E-cigarettes on health and on smoking trends will become apparent in the next decade.

The aging population of the world is another risk factor for cardiovascular disease and one which has no prescribed treatment. The developed countries, and to a certain extent the developing countries, have fallen victim to their own economic success. Improved quality of life, falling birth rates and longer life expectancies have resulted in increasingly old populations in the developed countries. In 2010, at least 20 % of the populations of the more industrialised countries were over the age of 65, and by 2050, one billion people will be over the age of 65 worldwide [69].

Age-related vascular changes have been well documented. These include luminal enlargement with wall thickening, arterial stiffness and endothelial dysfunction. Arterial stiffness is the reduced capability of a blood vessel to dilate and constrict in response to changes in pressure. Both a linear relationship between age and stiffness [70] as well as an accelerated stiffening between ages 50 and 60 have been described [71]. The aetiology of endothelial dysfunction in aging is multifaceted and includes a reduction in endothelial nitric oxide synthase activity leading to a reduction in endothelial vasodilation, as well as a decline in the integrity of the endothelium as a barrier and loss of the ability of endothelial cells to proliferate and migrate after tissue injury [72]. Aging is one CVD risk factor that cannot be curbed; however, new treatment strategies to fight the effects of aging might help alleviate the burden of an increasingly old population.

In 2008, around 40 % of adults had raised blood pressure [73], and it accounts for nearly 13 % of all deaths (7.5 million) worldwide [1]. Hypertension is a major risk factor for ischaemic heart disease (IHD) and haemorrhagic stroke with 54 % of stroke and 47 % of IHD attributable to hypertension. Eighty percent of this burden occurred in low-income and middle-income countries [74]. Moreover, blood pressure levels have been shown to be positively and progressively related to coronary heart disease and stroke [75]. In those older than 50, every increment of 20/10 mmHg results in a doubling of cardiovascular risk, starting as low as 115/75 mmHg [76]. This highlights the importance of effective control of blood pressure which might be addressed using a combination of antihypertensive drugs as well stressing the importance of compliance.

Dyslipidaemia is another major cardiovascular risk factor. In 2008, 39 % of adults had raised total cholesterol and an estimated 2.6 million deaths were attributed to this risk factor alone. In high-income countries, 50 % of the population had raised total cholesterol which is double that of low-income countries, with 2.6 million deaths annually [1]. The Framingham study first reported a link between high cholesterol and increased coronary heart disease in the 1960s [77], and more recently, lipoprotein (a) which is an LDL-like particle has been independently associated with CHD and stroke [78]. Various treatment strategies have aimed to reduce CVD risk in those with dyslipidaemia, but statins have been the most significant players in this field. Recent controversy around statin use has threatened to derail the success of preventing cardiovascular mortality by treating high cholesterol. The authors of a paper published in 2013 by the British Medical Journal [79] had indicated that statin therapy in low-risk individuals does not result in a reduction in all-cause mortality or serious illness whilst conveying an 18 % risk of side effects. The subsequent media reports have no doubt concerned physicians, as sensationalist headlines could potentially affect patient compliance with medication.

Cardiovascular disease is the leading cause of morbidity and mortality in people with diabetes, and diabetes is a significant contributor to cardiovascular risk. In 2001, just under a million deaths were directly caused by diabetes, and nearly 1.5 million deaths from ischaemic heart disease and 700,000 deaths from stroke were attributed to high blood glucose [80]. However, with the emergence of better treatment strategies and patient education, the tide might just be changing. In the past

two decades, the difference in CVD complications in people with and without diabetes has narrowed substantially. In 1990, the rates of acute myocardial infarction and stroke were three to four times higher in those with diabetes as compared with the general population; however, by 2010, this difference had been reduced to less than double that of the general population without diabetes [81]. Moreover, since the 1990s, there has been a 3–5 % decline in the rates of acute myocardial infarction, cardiovascular mortality and all-cause mortality in patients with diabetes [82]. This might be a result of earlier detection of diabetes, as well as more effective drugs with fewer side effects and a renewed emphasis on patient education.

Arguably, urbanisation has been the most significant contributor to the growing cardiovascular mortality worldwide. As of 2010, more than half of the world's population live in cities. The advent of globalisation and urbanisation coupled with the emergence of 21 megacities around the world (>10 million) has led to the realisation that inhabitants of cities are at a greater cardiovascular risk than their rural counterparts simply by the virtue of the fact that their lifestyles have changed beyond recognition. Reduced physical activity, the use of motorised transportation, air pollution, sedentary jobs, stress of commuting to work, increased rates of smoking and readily available 'junk food' consisting of high calorie and high salt and sugar foods with low nutritional value, all contribute to increases in blood pressure, obesity and cardiovascular risk in general [69]. Air pollution in particular has been linked with increased incident stroke risk [83], and high residential traffic exposure has been linked with increased blood pressure in a recent comprehensive meta-analysis of European population-based cohorts [84].

Cardiovascular diseases are no different to other disorders in that prevention is better than cure. The World Health Organization 'best buy' interventions for treatment and prevention of CVD would cost around 11–13 billion dollars annually which is a significant saving considering that in the next 25 years, the cost of not investing in CVD prevention and treatment is predicted to be as much as $47 trillion worldwide [69]. These 'best buys' include protecting people from tobacco smoke and banning smoking in public places, warning about the dangers of tobacco use, enforcing bans on tobacco advertising and sponsorship, raising taxes on tobacco, restricting access to retailed alcohol, enforcing bans on alcohol advertising, raising taxes on alcohol, reducing salt intake and salt content of food, replacing trans fat in food with polyunsaturated fat and promoting public awareness about diet and physical activity, including through mass media. These might seem intuitive and straightforward; however, pressure from multinational companies with vested interest and difficulty in changing lifestyle habits that have been formed over many years make it a formidable challenge and one which will not be easily achieved; however, in high-income countries, focus on prevention and improved treatment following cardiovascular events has resulted in significantly reduced rates of mortality [1].

References

1. Alwan A (2011) World Health Organisation: global status report on noncommunicable diseases 2010. World Health Organization, Geneva

2. Mendis S, Lindholm LH, Anderson SG et al (2011) Total cardiovascular risk approach to improve efficiency of cardiovascular prevention in resource constrain settings. J Clin Epidemiol 64:1451–1462
3. Mendis S, Puska P, Norrving B (2011) Global atlas on cardiovascular disease prevention and control. World Health Organisation, Geneva
4. Foundation BH (2014) Cardiovascular disease. (cited 24 Jun 2014); Available from: http://www.bhf.org.uk/heart-health/conditions/cardiovascular-disease.aspx
5. Mathers C, Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 3(11):e442
6. Woollard KJ, Geissmann F (2010) Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol 7(2):77–86
7. Moore KJ, Sheedy FJ, Fisher EA (2013) Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 13(10):709–721
8. Zernecke A, Bot I, Djalali-Talab Y et al (2008) Protective role of CXC receptor 4/CXC ligand 12 unveils the importance of neutrophils in atherosclerosis. Circ Res 102(2):209–217
9. Weber C, Noels H (2011) Atherosclerosis: current pathogenesis and therapeutic options. Nat Med 17(11):1410–1422
10. Zernecke A, Weber C (2012) Improving the treatment of atherosclerosis by linking anti-inflammatory and lipid modulating strategies. Heart 98(21):1600–1606
11. Hadi HA, Carr CS, Al Suwaidi J (2005) Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag 1(3):183–198
12. Clarkson P, Celermajer DS, Donald AE et al (1996) Impaired vascular reactivity in insulin-dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels. J Am Coll Cardiol 28(3):573–579
13. Skrha J, Vackva I, Kvasnicka J et al (1990) Plasma free N-terminal fibronectin 30-kDa domain as a marker of endothelial dysfunction in type 1 diabetes mellitus. Eur J Clin Invest 20(2):171–176
14. Hadi HA, Suwaidi JA (2007) Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag 3(6):853–876
15. Hamasaki S, Al Suwaidi J, Higano ST et al (2000) Attenuated coronary flow reserve and vascular remodeling in patients with hypertension and left ventricular hypertrophy. J Am Coll Cardiol 35(6):1654–1660
16. Yoshida M, Imalzumi T, Ando S et al (1991) Impaired forearm vasodilatation by acetylcholine in patients with hypertension. Heart Vessels 6(4):218–223
17. Taddei S, Virdis A, Ghiadoni L et al (2001) Age-related reduction of NO availability and oxidative stress in humans. Hypertension 38(2):274–279
18. Versari D, Daghini E, Virdis A et al (2009) The ageing endothelium, cardiovascular risk and disease in man. Exp Physiol 94(3):317–321
19. Virdis A, Ghiadoni L, Giannarelli C, Taddei S et al (2010) Endothelial dysfunction and vascular disease in later life. Maturitas 67(1):20–24
20. Stehouwer CD, Smulders YM (2006) Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. J Am Soc Nephrol 17(8):2106–2111
21. Prieto D, Contreras C, Sanchez A (2014) Endothelial dysfunction, obesity and insulin resistance. Curr Vasc Pharmacol 12(3):412–426
22. Toda N, Okamura T (2013) Obesity impairs vasodilatation and blood flow increase mediated by endothelial nitric oxide: an overview. J Clin Pharmacol 53(12):1228–1239
23. Gibbons GH, Dzau VJ (1994) The emerging concept of vascular remodeling. N Engl J Med 330(20):1431–1438
24. Mulvany MJ (2012) Small artery remodelling in hypertension. Basic Clin Pharmacol Toxicol 110(1):49–55
25. Endemann DH, Pu Q, DeCiuceis C et al (2004) Persistent remodeling of resistance arteries in type 2 diabetic patients on antihypertensive treatment. Hypertension 43(2):399–404
26. Schofield I, Malik R, Izzard A et al (2002) Vascular structural and functional changes in type 2 diabetes mellitus: evidence for the roles of abnormal myogenic responsiveness and dyslipidemia. Circulation 106(24):3037–3043

27. Rosei EA, Rizzoni D (2010) Small artery remodelling in diabetes. J Cell Mol Med 14(5):1030–1036
28. Rizzoni D, De Ciuceis C, Porteri E et al (2012) Structural alterations in small resistance arteries in obesity. Basic Clin Pharmacol Toxicol 110(1):56–62
29. De Ciuceis C, Porteri E, Rizzoni D et al (2011) Effects of weight loss on structural and functional alterations of subcutaneous small arteries in obese patients. Hypertension 58(1):29–36
30. Sun X, Belkin N, Feinberg MW (2013) Endothelial microRNAs and atherosclerosis. Curr Atheroscler Rep 15(12):372
31. Madrigal-Matute J, Rotllan N, Arand JF, Fernandez-Hernando C (2013) MicroRNAs and atherosclerosis. Curr Atheroscler Rep 15(5):322
32. Rayner KJ, Moore KJ (2012) The plaque "micro" environment: microRNAs control the risk and the development of atherosclerosis. Curr Atheroscler Rep 14(5):413–421
33. Zampetaki A, Dudek K, Mayr M (2013) Oxidative stress in atherosclerosis: the role of microRNAs in arterial remodeling. Free Radic Biol Med 64:69–77
34. Imanishi T, Akasaka T (2013) MicroRNAs in peripheral artery disease. Curr Top Med Chem 13(13):1589–1595
35. Koutsis G, Siasos G, Spengos K (2013) The emerging role of microRNA in stroke. Curr Top Med Chem 13(13):1573–1588
36. Hulsmans M, Holvoet P (2013) MicroRNAs as early biomarkers in obesity and related metabolic and cardiovascular diseases. Curr Pharm Des 19(32):5704–5717
37. Vavuranakis M, Kariori M, Vrachatis D et al (2013) MicroRNAs in aortic disease. Curr Top Med Chem 13(13):1559–1572
38. Quiat D, Olson EN (2013) MicroRNAs in cardiovascular disease: from pathogenesis to prevention and treatment. J Clin Invest 123(1):11–18
39. Celermajer DS (2008) Reliable endothelial function testing: at our fingertips? Circulation 117(19):2428–2430
40. Tousoulis D, Antoniades C, Stefanadis C (2005) Evaluating endothelial function in humans: a guide to invasive and non-invasive techniques. Heart 91(4):553–558
41. Sun C, Wang JJ, Mackey DA, Wong TY (2009) Retinal vascular caliber: systemic, environmental, and genetic associations. Surv Ophthalmol 54(1):74–95
42. Nguyen TT, Wong TY (2006) Retinal vascular manifestations of metabolic disorders. Trends Endocrinol Metab 17(7):262–268
43. Wong TY, Duncan BB, Golden SH et al (2004) Associations between the metabolic syndrome and retinal microvascular signs: the atherosclerosis risk in communities study. Invest Ophthalmol Vis Sci 45(9):2949–2954
44. Zhao Y, Yang K, Wang F et al (2012) Associations between metabolic syndrome and syndrome components and retinal microvascular signs in a rural Chinese population: the Handan Eye study. Graefes Arch Clin Exp Ophthalmol 250(12):1755–1763
45. Kawasaki R, Tielsh JM, Wang JJ et al (2008) The metabolic syndrome and retinal microvascular signs in a Japanese population: the Funagata study. Br J Ophthalmol 92(2):161–166
46. Ding J, Wai KL, McGeechan K et al (2014) Retinal vascular caliber and the development of hypertension: a meta-analysis of individual participant data. J Hypertens 32(2):207–215
47. Kawasaki R, Xie J, Cheung N et al (2012) Retinal microvascular signs and risk of stroke: the Multi-Ethnic Study of Atherosclerosis (MESA). Stroke 43(12):3245–3251
48. Cheung CY, Tay WT, Ikram MK et al (2013) Retinal microvascular changes and risk of stroke: the Singapore Malay Eye study. Stroke 44(9):2402–2408
49. Wang L, Wong TY, Sharrett AR et al (2008) Relationship between retinal arteriolar narrowing and myocardial perfusion: multi-ethnic study of atherosclerosis. Hypertension 51(1):119–126
50. Al-Fiadh AH, Farouque O, Kawasaki R et al (2014) Retinal microvascular structure and function in patients with risk factors of atherosclerosis and coronary artery disease. Atherosclerosis 233(2):478–484
51. De Silva DA, Manzano JJ, Liu EY et al (2011) Retinal microvascular changes and subsequent vascular events after ischemic stroke. Neurology 77(9):896–903

52. Taylor B, Rochtchina E, Wang JJ et al (2007) Body mass index and its effects on retinal vessel diameter in 6-year-old children. Int J Obes (Lond) 31(10):1527–1533
53. Cheung N, Saw SM, Islam FM et al (2007) BMI and retinal vascular caliber in children. Obesity (Silver Spring) 15(1):209–215
54. Murgan I, Beyer S, Kotliar KE et al (2013) Arterial and retinal vascular changes in hypertensive and prehypertensive adolescents. Am J Hypertens 26(3):400–408
55. Liew G, Mitchell P, Wong TY, Wang JJ (2012) Retinal microvascular signs are associated with chronic kidney disease in persons with and without diabetes. Kidney Blood Press Res 35(6):589–594
56. Finucane MM, Stevens GA, Cowan MJ et al (2011) National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 377(9765): 557–567
57. Gutierrez-Fisac JL, Regidor E, Banegas JR, Rodriguez A (2002) The size of obesity differences associated with educational level in Spain, 1987 and 1995/97. J Epidemiol Community Health 56(6):457–460
58. Martinez JA, Kearney JM, Kafatos A et al (1999) Variables independently associated with self-reported obesity in the European Union. Public Health Nutr 2(1A):125–133
59. Sundquist J, Johansson SE (1998) The influence of socioeconomic status, ethnicity and lifestyle on body mass index in a longitudinal study. Int J Epidemiol 27(1):57–63
60. van Lenthe FJ, Schrijvers CTM, Droomers M et al (2004) Investigating explanations of socioeconomic inequalities in health: the Dutch GLOBE study. Eur J Public Health 14(1):63–70
61. The NHS Information Centre LS (2011) Statistics on obesity, physical activity and diet: England, 2011. http://www.hsic.gov.uk. Published 24 Feb 2011
62. Greenstein AS, Khavandi K, Withers SB et al (2009) Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. Circulation 119(12):1661–1670
63. Gil-Ortega M, Stucchi P, Guzman-Ruiz R et al (2010) Adaptative nitric oxide overproduction in perivascular adipose tissue during early diet-induced obesity. Endocrinology 151(7): 3299–3306
64. Gao YJ, Lu C, Su L-Y et al (2007) Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide. Br J Pharmacol 151(3):323–331
65. Lee YC, Chang HH, Chiang CL et al (2011) Role of perivascular adipose tissue-derived methyl palmitate in vascular tone regulation and pathogenesis of hypertension. Circulation 124(10):1160–1171
66. Aghamohammadzadeh R, Greenstein AS, Yadav R et al (2013) Effects of bariatric surgery on human small artery function: evidence for reduction in perivascular adipocyte inflammation, and the restoration of normal anticontractile activity despite persistent obesity. J Am Coll Cardiol 62(2):128–135
67. Jha P, Chaloupka FJ (1999) Curbing the epidemic: governments and the economics of tobacco control. The World Bank. Tob Control 8(2):196–201
68. Critchley JA, Capewell S (2003) Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA 290(1):86–97
69. Laslett LJ, Alagona P Jr, Clark BA 3rd et al (2012) The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am Coll Cardiol 60(25 Suppl):S1–S49
70. Avolio AP, Chen SG, Wang RP et al (1983) Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 68(1):50–58
71. McEniery CM, Yasmin, Hall IR et al (2005) Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 46(9):1753–1760
72. North BJ, Sinclair DA (2012) The intersection between aging and cardiovascular disease. Circ Res 110(8):1097–1108