TAMPEREEN TEKNILLINEN YLIOPISTO
TAMPERE UNIVERSITY OF TECHNOLOGY

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Whole-body Electric Bioimpedance Measurement in the Evaluation of Vascular Function

Julkaisu 1389 • Publication 1389

Tampere 2016

Tampereen teknillinen yliopisto. Julkaisu 1389
Tampere University of Technology. Publication 1389

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Thesis for the degree of Doctor of Science in Technology to be presented with due permission for public examination and criticism in Tietotalo Building, Auditorium TB109, at Tampere University of Technology, on the 9th of September 2016, at 8.45 am.

Tampereen teknillinen yliopisto - Tampere University of Technology
Tampere 2016

ISBN 978-952-15-3760-8 (printed)
ISBN 978-952-15-3805-6 (PDF)
ISSN 1459-2045

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Abstract

Background: Two pathologies affecting the arterial wall, atherosclerosis and arterial stiffening, are strong predictors of cardiovascular diseases and mortality. The identification of these at the sub-clinical, asymptomatic stages is potentially useful for the prevention of cardiovascular risk. Arterial stiffness can be evaluated locally by measuring carotid artery elasticity or segmentally by measuring pulse wave velocity (PWV), and of these two methods, PWV is considered the gold standard for assessing arterial stiffness. Whole-body impedance cardiography (ICG_{WB}) has previously been shown to be a fast and operator-independent method to measure PWV, but the lack of reference values has limited its use in clinical practice. Moreover, the applicability of the ICG_{WB} method in measuring PWV in large-scale epidemiological studies has not been tested previously.

Carotid artery intima-media thickness (IMT) and brachial artery flow-mediated dilation (FMD) are well-known non-invasive markers of early atherosclerosis. Although the pathophysiology of atherosclerosis involves many features similar to arterial stiffness, whether IMT and FMD reflect similar or different aspects of vascular damage in comparison to PWV is not known. In addition, PWV and indices of carotid artery elasticity are often used interchangeably, but the relationship between these has received little interest to date.

Aims: The objective of the present study was to establish reference values for PWV as measured by ICG_{WB} and gain more insight into the association of PWV with the markers of sub-clinical atherosclerosis (IMT, FMD) and local arterial elasticity. In addition, the aim of the current study was to study the applicability of the ICG_{WB} method for measuring PWV in an epidemiological study. Furthermore, the objective of the present study was to develop a new integrated cardiovascular parameter reflecting several aspects of the cardiovascular system – i.e. arterial stiffness, arterial wall structure and cardiac pump function.

Subjects and Methods: The study population was combined from three distinct studies: 455 subjects from the Health 2000 Survey (supplemental study), 1872 subjects from the Cardiovascular Risk in Young Finns Study and 87 subjects from the Tampere Ambulatory Blood Pressure Study. Pulse wave velocity, stroke volume and systemic vascular resistance were measured from all subjects using the commercially available ICG_{WB} monitor (CircMon™). Indices of carotid artery elasticity and carotid artery IMT were measured by ultrasound in the Health 2000 Survey (supplemental study) and the Cardiovascular Risk in Young Finns Study. Moreover, brachial FMD was measured by ultrasound in the Cardiovascular Risk in Young Finns Study.

Results: In subjects aged 46–76 years, IMT was directly and independently associated with PWV, but in younger subjects, IMT and PWV were not independently correlated. Carotid artery distensibility was inversely and independently associated with PWV, whereas FMD and PWV were not independently related. Metabolic syndrome and several other cardiovascular risk factors were found to associate with increased PWV, a finding which is in line with previous epidemiological studies using different methods to measure PWV.

The present thesis introduces and evaluates a new ICG_{WB}-based hemodynamic parameter known as arterial tension time (ATT), which is defined as the time difference between the stroke-volume-introduced arterial distension and maximal integrated arterial distension. Decreased ATT was associated with increased arterial stiffness, increased subclinical atherosclerosis and decreased stroke volume. The current study also reports reference values for PWV measured by ICG_{WB} for males and females in different age groups with no evidence of cardiovascular disease and a low burden of risk factors.

Conclusion: The present study has four main findings. Firstly, the current study establishes reference values for ICG_{WB}-based PWV in an adult Finnish population. Reference values can be useful in the clinical management of patients in future studies. Secondly, PWV was not found to associate with IMT or FMD in young adults, but in older individuals, PWV and IMT were directly and independently correlated. Therefore, the current findings suggest that PWV may reflect a different aspect of vascular damage than FMD or IMT in young adults, whereas in older adults, the information provided by PWV and IMT may be, to some extent, similar. The present findings encourage the use of a

combination of complementary non-invasive methods to evaluate arterial wall alterations, particularly in young adults. Thirdly, ICG_{WB} provides a convenient and reliable tool for evaluating arterial stiffness in epidemiological studies. Fourthly, ATT developed in this study could potentially include information on several aspects of cardiovascular structure and function, and possibly serve as a new integrated parameter of cardiovascular health.

Preface

This study was conducted at the Department of Clinical Physiology and Nuclear Medicine at the Medical Imaging Centre of the Pirkanmaa Hospital District, and at the Department of Electronics and Communications Engineering at the Tampere University of Technology.

Firstly, I would like to acknowledge my supervisor, Professor Jari Hyttinen, whose expertise and guidance advanced this thesis invaluably. I would also like to express my sincere gratitude to my other supervisor, Professor Mika Kähönen, without whose motivation and encouragement I would not have finished this thesis.

I would like to thank my co-authors, Heikki Aatola, Nina Hutri-Kähönen, Antti Jula, Markus Juonala, Risto Kaaja, Katriina Kukkonen-Harjula, Terho Lehtimäki, Silja Majahalme, Leena Moilanen, Tuomo Nieminen, Olli T. Raitakari, Antti Reunanen, Veikko Salomaa, Kalle Sipilä, Väinö Turjanmaa, Jorma S.A. Viikari and Marko Virtanen, for their skilful contributions to the original publications. My sincere thanks also go to the reviewers, Professor Mart Min and Professor Tapio Seppänen, for their valuable comments.

Very special thanks go to Docent Tiit Kööbi for his support in methodological issues. Research nurse Pirjo Järventausta has been helpful with all practical issues related to the research, which is greatly acknowledged.

Last, but not least, I would like to thank my family for the support they provided through this project.

Tampere, Finland

May, 2016

Contents

Acronyms

ANOVA	Analysis of variance
ASI	Arterial stiffness index
ATT	Arterial tension time
CAC	Carotid artery compliance
cfPWV	Carotid-femoral pulse wave velocity
CO	Cardiac output
CRP	C-reactive protein
dist	Distensibility
ECG	Electrocardiogram
FMD	Flow-mediated dilation
HDL	High-density lipoprotein
ICG_{TH}	Thoracic impedance cardiography
ICG_{WB}	Whole-body impedance cardiography
IDF	International diabetes foundation
IMT	Intima-media thickness
IPG	Impedance plethysmogram
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
NCEP	National Cholesterol Education Program
NO	Nitric oxide
OGTT	Oral glucose tolerance test
PWV	Pulse wave velocity
SD	Standard deviation
SE	Standard error
SI	Stroke volume index
SV	Stroke volume
SVDI	Stroke volume distribution index
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
YEM	Young's elastic modulus
YFS	The Cardiovascular Risk in Young Finns Study

List of publications

This thesis is based on the following original publications:

I Koivistoinen T, Kööbi T, Jula A, Hutri-Kähönen N, Raitakari OT, Majahalme S, Kukkonen-Harjula K, Lehtimäki T, Reunanen A, Viikari J, Turjanmaa V, Nieminen T, Kähönen M. Pulse wave velocity reference values in healthy adults aged 26–75 years. Clinical Physiology and Functional Imaging. 2007;72:191-196.

II Koivistoinen T, Virtanen M, Hutri-Kähönen N, Lehtimäki T, Jula A, Juonala M, Moilanen L, Aatola H, Hyttinen J, Viikari JS, Raitakari OT, Kähönen M. Arterial pulse wave velocity in relation to carotid intima-media thickness, brachial flow-mediated dilation and carotid artery distensibility: the Cardiovascular Risk in Young Finns Study and the Health 2000 Survey. Atherosclerosis. 2012;220:387-393.

III Sipilä K, Koivistoinen T, Moilanen L, Nieminen T, Reunanen A, Jula A, Salomaa V, Kaaja R, Kööbi T, Kukkonen-Harjula K, Majahalme S, Kähönen M. Metabolic syndrome and arterial stiffness: the Health 2000 Survey. Metabolism. 2007;56:320-6.

IV Koivistoinen T, Kööbi T, Moilanen M, Jula A, Lehtimäki T, Hyttinen J, Kähönen M. Arterial tension time reflects subclinical atherosclerosis, arterial stiffness and stroke volume. Clinical Physiology and Functional Imaging. 2011;31:464-471.

Author's contributions

Original publications I, II and IV: The author planned analyses together with M. Kähönen, T. Kööbi and/or J. Hyttinen. The author analysed the results and wrote the manuscripts, which were commented on by the co-authors.

Original publication III: K. Sipilä was the corresponding author of the publication. The author cooperated with K. Sipilä in the planning and execution of analyses, and in the writing of the manuscript. The manuscript was commented on by the co-authors.

The author did not participated on subject selection or data collection in the Health 2000 Survey, in the Cardiovascular Risk in Young Finns Study or in the Tampere Ambulatory Blood Pressure Study.

1 Introduction

With aging and the accumulation of cardiovascular risk factors, two pathologies affect the arteries: atherosclerosis, a progressive disease characterised by the accumulation of lipids and fibrous elements in the arteries, and arteriosclerosis, an age-related stiffening and dilatation of large arteries. Studying these pathologies is essential, since atherosclerosis is the most common cardiovascular cause of death in the Western world (Lusis 2000, Nichols et al. 2011), and arterial stiffening (arteriosclerosis) has been shown to associate with increased cardiovascular risk in several patient groups (Lehmann et al. 1998, Blacher et al. 1999a,b, Amar et al. 2001) as well as in healthy subjects (Mattace-Raso et al. 2006).

Several different non-invasive methods have been developed to estimate structural and functional changes in the arteries. Brachial artery flow-mediated dilation (FMD) reflects early and predominantly functional atherosclerotic changes in the arterial wall, whereas carotid artery intima-media thickness (IMT) represents a marker of more advanced structural (atherosclerotic) changes (Ter Avest et al. 2007). Indices of local arterial elasticity and pulse wave velocity (PWV) measured between two arterial sites are, in turn, commonly used markers of arterial stiffness. Brachial FMD and carotid IMT are found to be inversely related (Hashimoto et al. 1999, Ravikumar et al. 2002, Juonala et al 2004), suggesting that both are representatives of the same atherosclerotic process. Previous studies on the association between PWV and carotid IMT or brachial FMD have been inconsistent (Liang et al. 1998, van Popele et al. 2001, Zureik et al. 2002, Nigam et al. 2003, Oren et al. 2003, Kobayashi et al. 2004, Soltesz et al. 2009, Gomez-Marcos et al. 2011), and it therefore remains unclear whether arterial stiffening, at least in its early stages, reflects the atherosclerotic process or an alternative pathology of the vascular wall (Zieman et al. 2005, Cecelja and Chowienczyk 2009). Moreover, PWV and indices of local arterial elasticity are often used interchangeably, but the relationship between these has received little interest to date. Studying the similarities and differences between these vascular biomarkers, which are parameters of subclinical cardiovascular

disease, could increase the estimation of the individual cardiovascular risk and improve strategies for effective prevention (Bruno et al. 2014).

PWV measured between the carotid and femoral artery has proven an independent predictor of cardiovascular events and mortality in several populations (Blacher et al. 1999a, Laurent et al. 2001, Shokawa et al. 2005, Mattace-Raso et al. 2006), and it is considered the gold-standard for assessing arterial stiffness (Laurent et al. 2006). The measurement of carotid-femoral PWV using mechanotransducers has been applied in most of the epidemiological studies demonstrating the predictive value of PWV for cardiovascular events (Laurent et al. 2006). The whole-body impedance cardiography method with an additional voltage sensing channel also provides a convenient and reliable tool for PWV measurement (Kööbi et al. 2003), but the lack of reference values has limited its use in clinical practice. In addition, the applicability of the whole-body impedance cardiography method for measuring PWV in large scale epidemiological studies has not been tested previously.

Stroke volume (SV), the amount of blood ejected from the heart to the circulation on every heartbeat, can be used as a surrogate marker of cardiac pump function. The SV-to-pulse-pressure ratio has been shown to associate with cardiovascular risk and cardiovascular events (de Simone et al. 1999, Lind et al. 2004, 2006), but whether SV predicts cardiovascular events has not been extensively studied. Moreover, although carotid IMT has been related to cardiovascular disease and cardiovascular events, there is also scepticism regarding the usefulness of carotid IMT as a risk stratification tool for the general population (Helfand et al. 2009, Lorenz et al. 2010). Furthermore, previous studies on the possible relationship between indices of carotid artery elasticity and cardiovascular events or mortality have reported inconclusive results (Störk et al. 2004, Dijk et al. 2005, Ogawa et al. 2009). Thus, ability of these indices of cardiovascular structure and function to predict cardiovascular risk is, to a degree, limited. It could hence be of clinical interest to develop an integrated cardiovascular parameter reflecting several aspects of the cardiovascular system – i.e. arterial stiffness, arterial wall structure and cardiac pump function – and thus possibly improve risk stratification.

The objective of the present thesis was to gain more insight into the association of PWV with the markers of subclinical atherosclerosis (brachial FMD, carotid IMT) and local arterial elasticity. The thesis also establishes reference values for PWV as measured by whole-impedance cardiography, and studies the applicability of the whole-body impedance cardiography method for

measuring PWV in an epidemiological study. In addition, the aim of the present study was to develop a new hemodynamic parameter based on whole-body impedance cardiography that reflects arterial wall structure and function as well as cardiac pump function.

2 Review of the literature

2.1 Structure and mechanical properties of the arterial wall

The artery wall consists of three distinct layers. The innermost layer (the intima) is a thin region of endothelial cells and extracellular connective tissue matrix. The middle layer (the media) consists of smooth muscle cells and a network of elastic and collagen fibrils, whereas the outer layer (the adventitia) is composed of connective tissues with interspersed fibroblasts and smooth muscle cells (Lusis 2000, Nichols et al. 2011) (Figure 2.1).

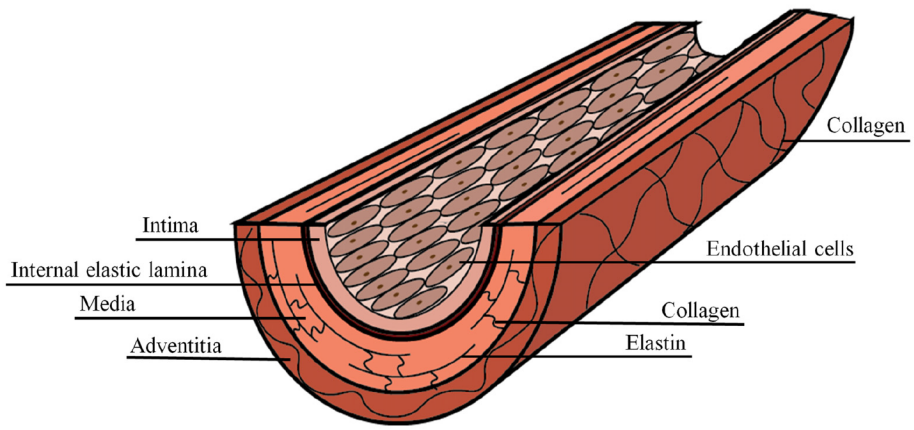

Figure 2.1: Composite structure of the artery.

Reprinted from Frontiers in Genetics, 6, Kohn JC, Lampi MC, Reinhart-King CA. Age-related vascular stiffening: causes and consequences, 112, Copyright (2015), with permission from Kohn, Lampi and Reinhart-King.

The endothelium regulates vascular tone and vascular permeability by sensing changes in hemodynamic forces and releasing a number of substances (Tomiyama and Yamashina 2010). Endothelial dysfunction is considered the

earliest marker of atherosclerosis (Veerasamy et al. 2015). The media comprises the majority of the arterial wall bulk and is responsible for its elastic properties, allowing the artery to expand and contract with the blood pulse (O'Rourke 1990, Kohn et al. 2015). Aging and the accumulation of cardiovascular risk factors result in several structural alterations in the media, including decreased elastin content, increased collagen content, a change in the type of collagen, and collagen cross-links from advanced glycation end products (Cecelja and Chowienczyk 2009, Prenner and Chirinos 2015), leading to the decreased elasticity of the arterial wall (Lakatta and Levy 2003). It should be noted that the endothelium regulates the smooth muscle tone of the arterial wall, and abnormalities of the endothelium may therefore also have role in the decreased elasticity of the artery (Lakatta and Levy 2003). The main function of the outer adventitia (60%–70% of adventitia thickness) is to support the artery and connect with surrounding tissue, whereas the inner adventitia plays an important role in opposing the transmural pressure and prevents the overdistension of the artery at high load (Chen et al. 2011).

2.2 Measurement of the arterial wall structure and function

2.2.1 Modelling the arterial circulation

The arterial tree has two functions – to deliver blood from the left ventricle to capillaries, and to cushion the pulsation generated by the heart (O'Rourke and Hashimoto 2007). Impairment in the cushioning function (i.e. increased stiffness/decreased compliance) is one of the earliest detectable manifestations of the adverse functional and structural changes within the arterial the wall (Cavalcante et al. 2011).

In its simplest form, the arterial system can be described in terms of parallel resistance and capacitance components (Dart and Kingwell 2001). The resistance element corresponds to the measured systemic vascular resistance (SVR), i.e. the vessel's tendency to oppose blood flow, whereas the capacitance element corresponds to the compliance (C) of the arterial circulation, i.e. the capacity of the arterial system to accommodate further increase in volume (Δ volume/Δ pressure) (Dart and Kingwell 2001):

$$SVR = MAP/CO \quad (1)$$

and

$$C = SV/PP \quad (2)$$

where MAP is mean arterial pressure, SV is left ventricle stroke volume, CO is cardiac output (heart rate * SV), and PP is pulse pressure (the difference between systolic and diastolic blood pressure).

This model has three major limitations in the estimation of total arterial compliance. Firstly, the model assumes that all pressure changes in circulation occur instantaneously, thus assuming that pulse wave velocity (PWV) is of infinite value (Dart and Kingwell 2001, Laurent et al. 2006). Secondly, it separates the "conduit" and "cushioning" functions of the arterial tree (Laurent et al. 2006), and, thirdly, it requires the measurement of SV (and PP) (McVeigh et al. 2002).

2.2.2 Local arterial elasticity

A simpler method to evaluate the cushioning function of the arteries is to measure local arterial elasticity. Parameters commonly used to characterise the (local) elastic behaviour of the arteries are compliance (C) and distensibility (dist), defined as the absolute (ΔV) and relative ($\Delta V/V$) change in local arterial volume (V) for a change in pressure (Δp):

$$C = \Delta V/\Delta p \quad (3)$$

and

$$dist = (\Delta V/V)/\Delta p \quad (4)$$

Since it is not possible to measure V and ΔV noninvasively and because the change in volume during the cardiac cycle is caused by a change in the luminal cross-sectional area (A) alone, compliance and distensibility can be expressed in terms of a change in A (Reneman and Hoeks 2000):

$$C = \Delta A/\Delta p \quad (5)$$

and

$$dist = (\Delta A/A)/\Delta p \quad (6)$$

Assuming that the arterial lumen is circular in cross-section, compliance and distensibility can also be rewritten in terms of diameter (Salomaa et al. 1995, Reneman and Hoeks 2000, Dijk et al. 2005, Nichols et al. 2011):

$$C = (D_s\text{-}D_d)/(P_s\text{-}P_d) \quad (7)$$

and

$$dist = [(D_s\text{-}D_d)/D_d]/(P_s\text{-}P_d) \quad (8)$$

where D_s is systolic diameter, D_d is diastolic diameter, P_s is systolic blood pressure, and P_d is diastolic blood pressure.

Some other terms have also been used to describe the (local) mechanical properties of the arteries. By definition, stress (σ) is the force applied/area to a particular object (Cavalcante et al. 2011). In arterial studies, σ per unit length is defined as pulse pressure divided by arterial wall thickness (h) (Reneman et al. 2005):

$$\sigma = (P_s\text{-}P_d)/h \quad (9)$$

Circumferential strain (ε) is the resulting deformation of an artery subjected to a stress force (Reneman et al. 2005, Cavalcante et al. 2011):

$$\varepsilon = (D_s\text{-}D_d)/D_d \quad (10)$$

Wall material can be characterized by Young's elastic modulus (YEM), which describes the ratio of stress to strain (Reneman et al. 2005, Cavalcante et al. 2011, Nichols et al. 2011):

$$YEM = \sigma/\varepsilon \quad (11)$$

or (from the Eq. 9 and 10):

$$YEM = [(P_s\text{-}P_d)\cdot D_d]/[(D_s\text{-}D_d)\cdot h] \quad (12)$$

The arterial stiffness index (ASI), also referred to as the β stiffness index, has been developed to reduce the impact of the curvilinear pressure-stiffness relationship on arterial stiffness, and it is therefore considered to be relatively

independent of blood pressure (Hirai et al. 1989, Salomaa et al. 1995, Juonala et al. 2005, Nichols et al. 2011):

$$ASI = [D_d \cdot \ln(P_s/P_d)]/(D_s - D_d). \quad (13)$$

It should be noted that the terms compliance and distensibility refer to the ease of distension, while stiffness (YEM, ASI) is the opposite. A stiff artery requires a high distending pressure for a given diameter increase (O'Rourke 1990).

Measurement of local arterial elasticity

The compliance, distensibility and stiffness of superficial arteries can be determined by ultrasound: a sound (pressure) wave is emitted, reflected by acoustic inhomogeneities and sensed, where the time delay between emission and reception is directly related to the depth of the interface (wave speed of 1540 m/s is almost the same for most tissues) (Nichols et al. 2011). When applied simultaneously to the posterior and anterior walls of the artery, direct information on the change in diameter over time (distension waveform) is provided (Figure 2.2). The generally used method to determine the diameter at diastole and stroke changes in diameter is video-image analysis, i.e. the measurement is recorded and the diameters are measured from the image clips by the operator.

Of the superficial arteries, carotid elasticity may be of particular interest, because atherosclerosis is frequent in that artery (Laurent et al. 2006). A major limitation of the local arterial elasticity measurement is the use of brachial artery blood pressure instead of central blood pressure. A pressure wave which propagates along the arterial tree with numerous branches is progressively amplified due to the wave reflections. The net result is that the amplitude of the pressure wave is higher in the peripheral arteries than the central arteries, and it is therefore inaccurate to use brachial pulse pressure as a surrogate for carotid pulse pressure, particularly in young subjects (Laurent et al. 2006).

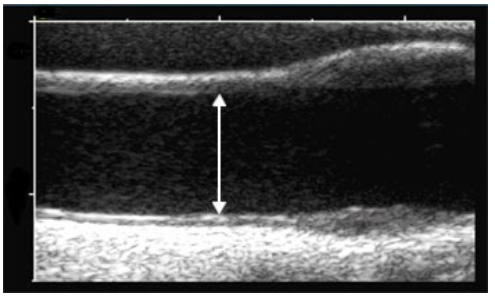

Figure 2.2: Diameter of the artery measured by ultrasound.

2.2.3 Segmental arterial stiffness

Left ventricle ejection generates a pressure pulse, which is propagated throughout the arterial tree. The speed of this pulse wave, i.e. pulse wave velocity (PWV), is determined by the elastic and geometric properties of the arterial wall and the blood density (Asmar et al. 1995). Since blood is incompressible, the major determinants of PWV are arterial wall thickness and lumen diameter (Asmar et al. 1995, Cavalcante et al. 2011). This concept can be formalised in a mathematical model by the Moens-Korteweg equation (Asmar et al. 1995, Laurent et al. 2006):

$$PWV = \sqrt{[(YEM \cdot h)/(2 \cdot \rho \cdot R)]} \quad (14)$$

or by the Bramwell-Hill equation (Asmar et al. 1995, Laurent et al. 2006):

$$PWV = \sqrt{[(\Delta P \cdot V)/(\Delta V \cdot \rho)]} \quad (15)$$

where YEM is Young's elastic modulus of the arterial wall (Eq. 12), h is wall thickness, R is arterial radius, ρ is blood density, ΔP is change in pressure, and ΔV is change in volume.

Thus, the propagation of the pulse wave is inversely related to the distensibility (Eq. 4) of the artery (Laurent et al. 2006). This propagation model is considered to be a more realistic model of the arterial tree than the simplified model described in chapter 2.2.1 (Laurent et al. 2006).

The Moens-Korteweg (Eq. 14) and Bramwell-Hill (Eq. 15) equations theoretically link PWV and arterial distensibility together. However, by

definition, PWV is the distance (ΔL) travelled by the pressure wave divided by the time (Δt) it takes for the wave to travel that distance:

$$PWV = \Delta L/\Delta t \quad (16)$$

This direct measurement of PWV (Eq. 16) corresponds to the progative model of the arterial system (Eq. 14 and 15) (Laurent et al. 2006, Townsend et al. 2015).

Measurement of segmental arterial stiffness

As discussed in the Expert Consensus Document on Arterial Stiffness (Laurent et al. 2006), PWV is generally accepted as the simplest, most robust and reproducible method to measure (segmental) arterial stiffness. In the clinical and epidemiological settings, PWV is measured between two arterial sites using the foot-to-foot velocity method (Figure 2.3) from pressure (Asmar et al. 1995), distension (van der Heijden-Spek et al. 2000) or Doppler (Cruickshank et al. 2002) waves. PWV can be calculated when the transit time (Δt) between the feet of the two waveforms and distance (ΔL) covered by the waves are known (Eq. 16).

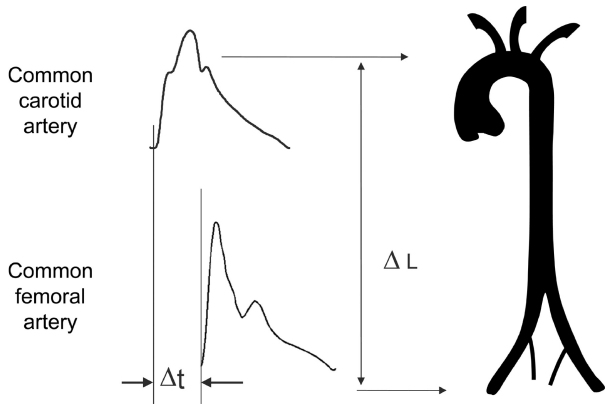

Figure 2.3: Measurement of PWV between the carotid and femoral artery with the foot-to-foot method.

Reprinted from European Heart Journal, 27, Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. Expert concensus document on arterial stiffness: methodological issues and clinical applications, 2588-2605, Copyright (2006), with permission from Oxford University Press.

Several different pathways have been used to measure PWV: carotid to femoral artery (Blacher et al. 1999a, Laurent et al. 2001, Shokawa et al. 2005, Mattace-Raso et al. 2006), subclavian artery to abdominal aorta (Cruickshank et al. 2002, Anderson et al. 2009), carotid to radial artery (Pannier et al. 2005), femoral to posterior tibial artery (Pannier et al. 2005), and brachial to tibial artery (Sugawara et al. 2005). Of these, the carotid to femoral artery PWV (cfPWV) has been shown to be an independent predictor of cardiovascular events and mortality in several populations (Blacher et al. 1999a, Laurent et al. 2001, Shokawa et al. 2005, Mattace-Raso et al. 2006), and it is considered the gold standard for assessing arterial stiffness (Laurent et al. 2006). Reference values for cfPWV in European (Mattace-Raso et al. 2010) and Latin-American (Diaz et al. 2014) populations, as well as reference values for brachial-ankle (brachial to tibial artery) PWV in a Chinese population (Ai et al. 2011), have been published previously.

Measurement devices

The Complior System (Colson, Les Lilas, France), evaluated in 1995 (Asmar et al. 1995), has been used in most of the epidemiological studies demonstrating the predictive value of PWV for cardiovascular events (Laurent et al. 2006, Townsend et al. 2015). The Complior System uses pressure transducers for automatic measurement of PWV. Pressure waveforms are digitized at different rates according to the distance between two recording sites; the sampling acquisition frequency is 500 Hz for carotid-femoral and 800 Hz for carotid-radial PWV. The two pressure waveforms are stored in a recirculating memory buffer, and a maximum of 588 data points per waveform are displayed at any given time. When the operator observes a pulse waveform of sufficient quality on the computer screen, digitization is suspended and the transit time is determined by means of a correlation algorithm between each simultaneously recorded wave (Asmar et al. 1995).

In the SphygmoCor (ArtCor, Sydney, Australia) system, a single pressure transducer is used to obtain a pulse sequentially from the carotid and femoral arteries with a short time apart. The time between the R-wave on the ECG and the proximal (carotid) pulse is subtracted from the time between the R-wave on the ECG and the distal (femoral) pulse to obtain the pulse transit time and to calculate PWV (Laurent et al. 2006).

Aortic PWV can be measured between two flow pulses simultaneously recorded by continuous Doppler ultrasound probes. The first probe is located at the root of the left subclavian artery, and the other at the level of abdominal aorta, above its bifurcation. Recordings are averaged over 45 to 120 cardiac cycles and transit time is automatically calculated following an automatic recognition of the foot of the pulse (Cruickshank et al. 2002, Laurent et al. 2006). Magnetic resonance imaging has also been used to measure PWV, and its potential advantage is a more accurate determination of the path length (Bolster et al. 1998, Redheuil et al. 2010). However, the relatively high cost per measurement and poor availability have restricted its use.

Effects of blood pressure and heart rate

The arterial stiffness varies as a function of its internal pressure – the stiffness is lower at a low and higher at a high pressure in a curvilinear fashion (O'Rourke and Mancia 1999). Therefore, the most significant physiological variable affecting PWV is the arterial distending pressure, i.e. mean arterial pressure (Townsend et al. 2015). This pressure dependence should be taken into consideration when comparing populations with different blood pressures. Another significant confounder of PWV is heart rate. Tachycardia (i.e. high heart rate) shortens the time available for recoil, which results in arterial stiffening (Lantelme et al. 2002)

Relationship between pulse wave velocity and carotid artery distensibility

Although PWV and carotid artery distensibility are theoretically linked (Eq. 14 and 15) and they are often used interchangeably in clinical studies, their physical definitions are not identical. Distensibility is directly measured from the carotid artery and is therefore a parameter that can be quantified and have units of measurement. In contrast, PWV measures the velocity of the pulse wave between two arterial sites and thus provides an indirect measure of a change in the mechanical properties of an arterial segment (Cohn et al. 2004, Hughes et al. 2004). Moreover, in subjects with high blood pressure and/or diabetes, the aorta stiffens more than the carotid artery with age and other cardiovascular risk factors (Paini et al. 2006). Therefore, it has been suggested that aortic stiffness

and carotid artery distensibility cannot be used as interchangeable predictors in high-risk patients (Laurent et al. 2006).

2.2.4 Other methods to measure arterial stiffness

As described in section 2.2.1, the stroke volume (SV) to pulse pressure (PP) ratio can be used as a crude estimate of systemic arterial compliance (or stiffness). The main limitation is the difficulty to accurately and non-invasively determine SV and PP in the ascending aorta.

The arterial pressure wave is reflected at branch points and areas of alteration in arterial stiffness. Thus, the arterial pressure waveform is a composite of the stroke-volume-induced pressure wave and a reflected wave. In stiff arteries, PWV is higher and the early return of the reflected waves leads to an increase in systolic blood pressure. The Augmentation index (AIx) describes this phenomenon, and it is determined from the arterial pressure wave as a ratio of augmentation pressure and pulse pressure (Laurent et al. 2006). AIx is typically measured from the radial artery, using a transfer function, or from the carotid artery. Several different factors – such as the timing of the reflected wave as well as age, height, sex, heart rate, the shape of the forward wave, and left ventricular outflow – influence AIx (Kingwell and Gatzka 2002), and it is therefore not a true indicator of arterial stiffness.

In the "area method", aortic blood flow is measured using a velocimeter at the suprasternal notch and associated driving pressure by means of applanation tonometry over the carotid artery. Moreover, peripheral blood pressure is measured from the brachial artery. A mathematical conversion is then used to calculate systemic arterial compliance (Dart et al. 2006). Arterial compliance as measured with this method has not been shown to predict cardiovascular events (Laurent et al. 2006).

2.2.5 Endothelial function and wall thickness

The endothelium regulates vascular tone and vascular permeability by sensing changes in hemodynamic forces and releasing a number of substances, and of these, nitric oxide (NO) has a pivotal role in protecting against the initiation and progression of atherosclerosis (Verma and Anderson 2002, Tomiyama and Yamashina 2010). Brachial artery flow-mediated dilation (FMD), the most

frequently used surrogate marker of endothelial function, measures NO-dependent vasodilatation after artificially induced hypoxia. It is considered to reflect early and predominantly functional atherosclerotic changes in the arterial wall (Ter Avest et al. 2007, Tomiyama and Yamashina 2010). In this method, increased blood flow is induced by the inflation of a pneumatic tourniquet placed around the forearm to a pressure of over 250 mmHg for up to 5 minutes, followed by release. Brachial artery diameter is measured by the operator from stored ultrasound image clips at rest and after cuff release (Figure 2.4).

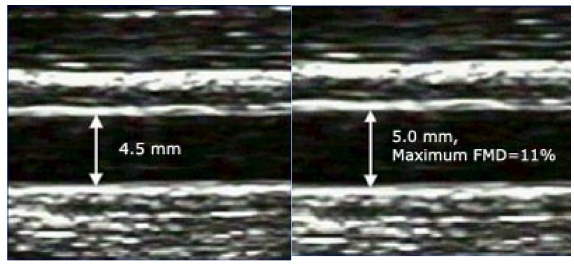

Figure 2.4: Measurement of brachial artery flow-mediated dilation (FMD) by ultrasound. Brachial artery diameter at rest (left) and after cuff release (right).

In contrast to brachial FMD, carotid artery intima-media thickness (IMT), a widely used measure of atherosclerosis, represents a marker of more advanced structural changes (Ter Avest et al. 2007). IMT detected by high-resolution ultrasound represents the combined width of the intima and media, which are technically indistinguishable (Bruno et al. 2014). Moreover, the assessment of wall thickness is limited to the intima and media, because the adventitia cannot be distinguished reliably from the surrounding structures (Figure 2.5) (Reneman and Hoeks 2000). The measurement of brachial FMD and carotid IMT are described in more detail in section 4.2.5.

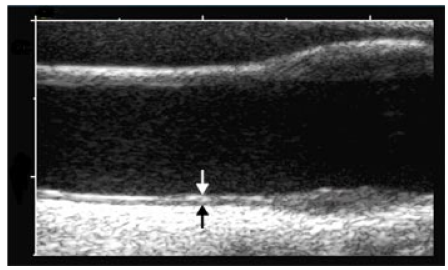

Figure 2.5: Measurement of carotid artery intima-media thickness (IMT) by ultrasound.

Arterial wall thickness (h) is included in the Moens-Korteweg equation (Eq. 14) and, therefore, in theory, PWV should increase with the increase in IMT. However, previous studies on the association between PWV and carotid IMT have been inconsistent (Liang et al. 1998, van Popele et al. 2001, Oren et al. 2003, Kobayashi et al. 2004, Gomez-Marcos et al. 2011). There are two plausible reasons for these conflicting findings. Firstly, arterial radius (R) is included in the Moens-Korteweg equation (Eq. 14). Arteries dilate with aging (O'Rourke and Hashimoto 2007), which leads to increased R and possibly to a diluted relationship between PWV and IMT (Eq. 14). Secondly, Zureik et al. (2002) have previously shown that carotid atherosclerotic plaques, but not diffuse intima-media thickening, are positively associated with PWV. Since plaques are markers of more advanced atherosclerotic changes, we may speculate that PWV reflects the atherosclerotic process after a certain level. This assumption is supported by the previous negative findings on the association between brachial FMD and PWV (Liang et al. 1998, Nigam et al. 2003).

2.3 Impedance cardiography

The electrical impedance (Z) of biological materials can be understood as a form of pure resistance (R) (Kauppinen 1999). R for a cylindrical object of resistivity ρ is a function of the cross-sectional area (A) and length (l):

$$R = \rho \cdot l/A \tag{17}$$

R can also be given in terms of segmental volume (v):

$$R = \rho \cdot l^2/v \tag{18}$$

Assuming that both arteries and surrounding tissue can be approximated as cylindrical electrical conductors placed in parallel alignment, the pulsatile flow of blood can be modelled as the resistance of the blood pulse (R_b), in parallel with the steady basal value of resistance (R_0) of the surrounding tissue. Overall resistance (R_n) is given by (Kauppinen 1999):

$$R_n = (R_0 \cdot R_b)/(R_0+R_b) \quad (19)$$

The resistance change ΔR due to the addition of blood volume Δv is derived from equation 18 (Kauppinen 1999):

$$\Delta R=R_n-R_0=\rho \cdot l^2 \cdot [(v_1-v_0)/(v_0 \cdot v_1)]=-(\rho \cdot l^2 \cdot \Delta v)/(v_0 \cdot v_1)=-(\rho \cdot l^2/v^2) \cdot \Delta v \quad (20)$$

where v_0 is the original volume of the object and v_1 the volume after the addition of blood, which for small changes in v is $v_0 \approx v_1$. Thus, the relationship between the volume of a blood pulse and the related resistance change can be rewritten as:

$$\Delta R = - R^2 \cdot \Delta v/(\rho \cdot l^2) \rightarrow \Delta v = - \Delta R \cdot (\rho \cdot l^2)/R^2 \quad (21)$$

Thoracic impedance cardiography

Thoracic impedance cardiography (ICG_{TH}) was first described by Patterson et al. (1964), with further elaboration by Kubicek et al. (1966), to provide a continuous measurement of stroke volume (SV) for astronauts in NASA missions. With this method, four band electrodes are applied to the thoracic area. The outer electrodes supply the current (4 mA) and the inner electrodes are used to measure voltage changes. The measured changes in bio-impedance are related to changes in cardiac-related blood volume, and a mathematical conversion, based on equation 21 and empirical tuning, is used to translate the change in bio-impedance into SV (Patterson 1989, Geerts et al. 2011):

$$SV = \rho \cdot (L^2/Z_0^2) \cdot (dZ/dt) \cdot T \quad (22)$$

where ρ is the electrical resistivity of blood, L is the mean distance between the two inner electrodes, Z_0 is basal impedance and T is the ventricular ejection time. ΔR (from the equation 21) is replaced by the first derivative (dZ/dt) of the amplitude of the heart synchronous impedance variation (ΔZ). Cardiac output (CO) is calculated by multiplying SV by heart rate.

In the 1970s, Tishchenko (1973) introduced the whole-body impedance cardiography (ICG_{WB}) method. ICG_{WB} differs from ICG_{TH} in its placement of electrodes, the frequency of the alternating current used and the SV equation (Kööbi 1997a):

$$SV = k \cdot H^2 \cdot [(dZ/Z_c)/Z_0] \cdot (C/D) \quad (23)$$

where k is the empirical correction factor (including blood resistivity, the relation between the distance of voltage electrodes, and body height [k = 0.275 for males and k = 0.247 for females]), H is the subject's height, dZ is the amplitude of heart synchronous impedance variation, Z_C is the calibration factor, Z_0 is the baseline impedance of the body, C is the duration of the cardiac cycle, and D is the duration from the lowest value of whole-body impedance to the onset of the next cardiac cycle.

In ICG_{WB}, a pair of electrically connected electrodes is applied to the wrists and another to the ankles (Figure 2.6). The frequency of the alternating current applied in ICG_{WB} (30 kHz) is considerably lower than the frequency usually used in ICG_{TH} (70-200 kHz) (Kööbi et al. 1997a).

ICG_{WB} can also be used to measure PWV by adding a pair of electrodes on the knee joint level and the calf (Figure 2.6). That can be used to obtain the time delay of the pulse wave in the arterial tree. A commercially available ICG_{WB} monitor CircMon B202 (CircMon, JR Medical Ltd, Tallinn, Estonia) estimates the foot of the ICG signal that coincides with pulse transmission in the aortic arch, and, later, the foot of the impedance plethysmogram (IPG) signal that coincides with pulse transmission in the popliteal artery (Kööbi et al. 2003). By means of measured pulse transit time and estimated distance between these two sites, the CircMon software calculates PWV using the Equation 16 (Figure 2.6). The measurement of ICG_{WB} is described in more detail in section 4.2.3.

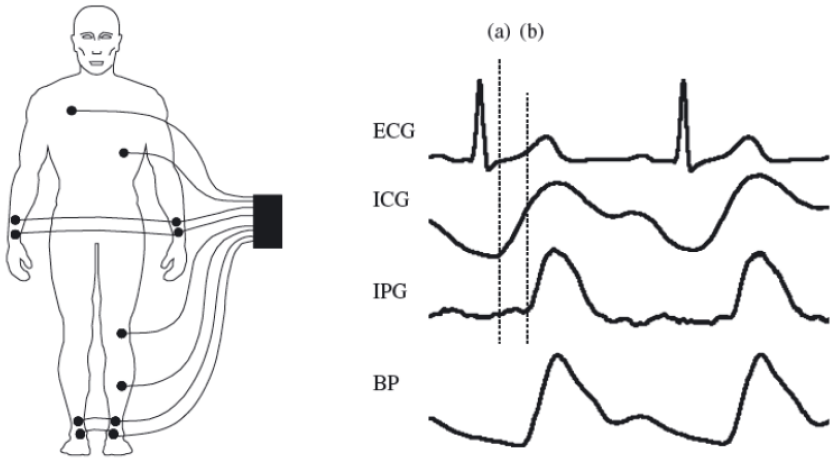

Figure 2.6: Left: Placement of electrodes in ICG_{WB} with an additional voltage sensing channel on the left calf for PWV measurement. Right: Synchronous recording of electrocardiogram (ECG), whole-body impedance cardiogram (ICG), impedance plethysmogram of the popliteal artery (IPG) and blood pressure (BP). Time difference between the feet of the ICG (a) and IPG (b) indicates the pulse transit time from the aortic arch to the popliteal artery.

Reprinted from Clinical Physiology and Functional Imaging, 27, Koivistoinen T, Kööbi T, Jula A, Hutri-Kähönen N, Raitakari OT, Majahalme S, Kukkonen-Harjula K, Lehtimäki T, Reunanen A, Viikari J, Turjanmaa V, Nieminen T, Kähönen M. Pulse wave velocity reference values in healthy adults aged 26-75 years, 191-196, Copyright (2007) with permission from John Wiley and Sons.

ICG_{WB} overestimates PWV values when compared to the Doppler method, and this small bias can be corrected using the empirical equation (Kööbi et al. 2003):

$$PWV = 0.696 \cdot PWVicg + 0.864 \quad (24)$$

A previous study (Tahvanainen et al. 2009) has shown good repeatability and reproducibility indexes for PWV as measured by CircMon (99 % and 87 %, respectively). Moreover, ICG_{WB} is a simple and operator-independent method to asses PWV. However, the absence of reference values has limited its use in clinical practice.

Limitations of impedance cardiography

The major limitation of impedance cardiography is the oversimplification of the physiological system. Stroke volume is equal to the change in the left ventricular volume during systole, whereas time-varying changes in impedance (dZ) reflect the integrated combination of volume changes in different tissues and organs (Kauppinen et al. 1998, Kauppinen et al. 1999, de Waal et al. 2008). For example, it is suggested that up to 55% of the time-varying signal originates from the skeletal muscles (Kauppinen et al. 1998). Moreover, heart-related amplitude variations in the ICG_{WB} signal originate evenly from various body segments, the trunk slightly more than the arms or legs (Kauppinen et al. 2000). Furthermore, inaccuracies can result from irregular cardiac rhythms, motion artefacts and valvular heart diseases (de Waal et al. 2008). However, several studies (Kööbi et al. 1997a, Kööbi et al. 1997b, Kööbi et al. 1999) using the Equation 23 for SV calculation, have shown that ICG_{WB} accurately measures CO when compared with the thermodilution method in different conditions (in the supine position, during a head-up tilt, after anaesthesia induction, after coronary artery by-pass surgery).

2.4 Cardiovascular risk factors and pulse wave velocity

Cardiovascular risk factors have several adverse effects on the arterial wall structure. Hyperglycaemia (i.e. high blood glucose) and hyperinsulinaemia (i.e. high blood insulin) promote the development of wall hypertrophy and fibrosis (Stehouwer et al. 2008). In addition, hyperglycaemia causes the cross-linking of collagen (Stehouwer et al. 2008, Prenner and Chirinos 2015). Moreover, hypertension results in increased collagen content, a change in the type of collagen and decreased elastin content (Cecelja and Chowienczyk 2009). Furthermore, cardiovascular risk factors cause low-grade inflammation and endothelial dysfunction (Stehouwer et al. 2008, Townsend et al. 2015). These changes have negative effects on the elastic properties of the arterial wall, and it is therefore reasonable to assume that cardiovascular risk factors also influence PWV.

Indeed, several different cardiovascular risk factors have been previously associated with increased cfPWV, with varying intensities. In the review by Cecelja and Chowienczyk (2009), age and blood pressure were associated with

cfPWV in 91% and 90% of the reviewed studies, respectively. The presence of diabetes mellitus and sex was associated with cfPWV in a respective 52% and 27% of the studies, while smoking and body mass index (BMI) were associated with cfPWV in 14% and 13% of the studies, respectively. Furthermore, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were significantly associated only in a respective 5% and 11% of the reports. Only one (3%) study reported a significant association with triglyceride levels (Cecelja and Chowienczyk 2009).

Metabolic syndrome (MetS) is a constellation of several cardiovascular risk factors including hypertension, obesity, glucose intolerance and dyslipidaemia. MetS has been shown to be a predictor of type 2 diabetes mellitus (Lorenzo et al. 2003), coronary heart disease (Bonora et al. 2003) and mortality (Isomaa et al. 2001). MetS has various definitions, and of these, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III definition (Expert panel 2001) and the International Diabetes Federation (IDF) definition (Alberti et al. 2005) are widely used. The individual components of MetS, as well as MetS as a whole, have been previously associated with arterial stiffness (Ferreira et al. 2005, Li et al. 2005, Schillaci et al. 2005).

The relationship between cardiovascular risk factors and PWV as measured by ICG_{WB} has not been studied previously. ICG_{WB} with an additional voltage-sensing channel to measure PWV has been shown to be well in agreement with the Doppler ultrasound method (Kööbi et al. 2003). Therefore, our hypothesis in the present study was that the associations between cardiovascular risk factors and PWV (measured by ICG_{WB}) would be similar to those found in previous studies using different methods to measure PWV.

2.5 Risk prediction

Although carotid IMT has been related to cardiovascular disease and cardiovascular events, there is also scepticism regarding the usefulness of carotid IMT as a risk stratification tool for the general population (Helfand et al. 2009, Lorenz et al. 2010). Moreover, the SV-to-pulse pressure ratio has been shown to associate with cardiovascular risk and cardiovascular events (de Simone et al. 1999, Lind et al. 2004, 2006), but whether SV predicts cardiovascular events has not been extensively studied.

Previous studies on the possible relationship between indices of carotid artery elasticity and cardiovascular events or mortality have reported inconclusive results. Ogawa et al. (2009) found an association between ASI and the presence of silent cerebral infarction in haemodialysis patients. In addition, Störk et al. (2004) have shown that YEM is associated with cardiovascular mortality in a population of older men. However, in a population of more than 2000 patients with manifest cardiovascular disease, indices of carotid elasticity (compliance, distensibility, YEM) were not independently related to the occurrence of vascular events (Dijk et al. 2005).

Therefore, the ability of these indices of cardiovascular structure and function to predict cardiovascular risk is, to a degree, limited. It could hence be of clinical interest to develop an integrated cardiovascular parameter reflecting several aspects of the cardiovascular system – i.e. arterial stiffness, arterial wall structure and cardiac pump function – and thus possibly improve risk stratification.

3 Aims of the study

The specific aims of the present thesis are as follows:

To establish reference values for ICG_{WB}-based PWV in an adult population (original publication I)

To examine PWV in relation to non-invasive measures of early atherosclerosis and local arterial elasticity (original publication II)

To test the applicability of the ICG_{WB} method for measuring PWV in a large epidemiological study (original publication III)

To develop a new ICG_{WB}-based hemodynamic parameter and to study its associations with traditional cardiovascular risk factors, as well as with ultrasound- and ICG_{WB}-derived indices of cardiovascular structure and function (original publication IV)

4 Subjects and methods

4.1 Subjects

The whole study population consisted of 1872 young adults participating in the Cardiovascular Risk in Young Finns Study, of 87 middle-aged men participating in the Tampere Ambulatory Blood Pressure Study, and of 455 older adults participating in the Health 2000 Survey (Table 4.1).

Table 4.1: Study populations in different sub-studies.

Study	Source of study population	Number of subjects
PWV reference values (Study I)	The Health 2000 Survey, the Cardiovascular Risk in Young Finns Study, and the Tampere Ambulatory Blood Pressure Study	799
PWV in relation to other indices of vascular status (Study II)	The Health 2000 Survey, and the Cardiovascular Risk in Young Finns Study	2090
Relationship between PWV and cardiovascular risk factors (Study III)	The Health 2000 Survey	401
Arterial tension time (Study IV)	The Health 2000 Survey	336

The Health 2000 Survey

The Health 2000 Survey was a large Finnish health examination survey carried out in 2000–2001 (Aromaa and Koskinen 2004). The overall study cohort was a two-stage stratified cluster sample (8028 subjects) representing the entire Finnish population aged 30 years and older. 1867 subjects participated in a

supplemental study (10–23 months after the Health 2000 Survey), and of these subjects, 455 (aged 46–76 years, 44.2% males) participated in ICG_{WB} measurement.

The Cardiovascular Risk in Young Finns Study

The Cardiovascular Risk in Young Finns Study (YFS) is an on-going multicentre study of atherosclerosis risk in Finnish children and young adults (Raitakari et al. 2008). The first cross-sectional survey was conducted in 1980 (n=3596). Thereafter, several follow-up studies have been performed. In 2003–2004, we examined the hemodynamic parameters of 257 subjects (aged 25–42 years, 46.7% males). In the 27-year follow-up in 2007, 1872 subjects (aged 30–45 years, 45.8% males) participated in ICG_{WB} monitoring.

The Tampere Ambulatory Blood Pressure Study

At baseline, 97 healthy untreated male volunteers were recruited at routine health check-ups offered for all individuals aged 35, 40 and 45 years at the Community Health Care Centre of the City of Tampere between 1987 and 1991 (Jokiniitty et al. 2002). After a mean of 10.8 years (range 8.8–12.3 years), 87 subjects (aged 44–57 years) participated in the follow-up visit also including ICG_{WB} measurement.

4.1.1 Study populations

Study I

The study population (n=799, age range 25–76 years, 51.1% males) was combined from three distinct studies: 455 subjects from the Health 2000 Survey (supplemental study), 257 from the YFS (2003–2004 sub-population follow-up) and 87 from the Tampere Ambulatory Blood Pressure study. To generate a healthy sample of subjects, the following exclusion criteria were used: abnormal body weight (BMI < 18.5 or ≥ 30 kg/m2); drug treatment for hypertension; current smoking; treatment for dyslipidaemia or fasting serum total cholesterol

> 6.1 mmol/l in subjects under 30 years of age, > 6.9 mmol/l in subjects aged 30–49 years and > 7.8 mmol/l in subjects aged 50 years or older (Rustad et al. 2004); diagnosed diabetes or fasting plasma glucose ≥ 7.0 mmol/l; or coronary heart disease. The exclusion was based on medical history, physical examination, biochemical tests and ECG. After exclusion, 283 subjects (aged 26–75 years, 45.9% males) with PWV data were available.

Study II

The first study cohort included those 1754 non-pregnant subjects (aged 30–45 years, 45.7% males) who participated in the YFS 2007 follow-up and for whom PWV, brachial and carotid ultrasound as well as and cardiovascular risk factor data were available. Of these, 123 subjects (7.0%) were on antihypertensive, 19 (1.1%) on anti-diabetic and 38 (2.2%) on lipid-lowering medication. The second study cohort included those 336 subjects (aged 46–76 years, 43.2% males) who participated in the Health 2000 Survey (supplemental study) and whose PWV, carotid ultrasound and cardiovascular risk factor data were available. Of these, 25 subjects (7.4%) had self-reported cerebrovascular disease, coronary heart disease or a history of myocardial infarction. 94 subjects (28.0%) were on antihypertensive, 13 (3.9%) on anti-diabetic and 32 (9.5%) on lipid-lowering medication.

Study III

Four hundred and one subjects (aged 46–76 years, 43.9% males) participated in ICG_{WB} measurement and an oral glucose tolerance test (OGTT) in the Health 2000 Survey (supplemental study). To generate a sub-sample of individuals free of cardiovascular diseases and diabetes, subjects with a previous myocardial infarction or stroke, or with diagnosed diabetes, coronary heart disease, cardiac insufficiency, cardiac arrhythmia, hypertension, arterial stenonis or thrombosis in a lower limb or other cardiovascular disease, were excluded. In addition, subjects who had a fasting plasma glucose concentration of 7 mmol/l or higher or who had a 2-hour glucose value of 11.1 mmol/l or higher in OGTT were excluded. Moreover, subjects who were on antihypertensive medication or statins were excluded. Thus, 200 subjects comprised the sub-sample population.

Study IV

The study cohort included those 336 subjects (aged 46–76 years, 43.2% males) who participated in the Health 2000 Survey (supplemental study) and whose systemic hemodynamics, carotid ultrasound and cardiovascular risk factor data were available.

4.2 Methods

4.2.1 Medical examination, questionnaires and laboratory analyses

In the Health 2000 Survey supplemental study, blood pressure was measured using a Finapres digital plethysmograph (Ohmeda, Engelwood, CO) or an automatic Omron manometer (Omron, Matsusaka, Japan and Omron Healthcare Europe, Hoofddorp, the Neatherlands). With Finapress, an average blood pressure value of 30-second measurement was used and results were verified by an Omron manometer. With Omron, the mean of three measurements was used. In YFS and in the Tampere Ambulatory Blood Pressure Study, blood pressure was measured with a random zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, United Kingdom), and the mean of three measurements was used. Height and weight were measured, and BMI was calculated by dividing the weight in kilograms by the square of the height in meters. Waist circumference was not measured in the Health 2000 Survey supplemental study, and Health 2000 Survey data was therefore used for waist circumference. Smoking habits were ascertained with a questionnaire, and smoking was defined as smoking on a daily basis. In the Health 2000 Survey supplemental study, smoking data was not available and it was collected from the Health 2000 Survey data. Venous blood samples were collected after an overnight fast, and all laboratory analyses were performed according to standardized protocols. The OGTT (Study III) was carried out after 10 to 12 hours of fasting. The subjects were given 75 g of glucose in a 10% solution, and venous blood samples for glucose and insulin determinations were taken before and 2 hours after the glucose load.

4.2.2 Metabolic syndrome

According to the NCEP definition (Expert panel 2001), three or more of the following criteria constitute a diagnosis of MetS: 1) waist circumference of ≥ 102 cm in men and ≥ 88 cm in women; 2) triglycerides ≥ 1.7 mmol/l; 3) HDL cholesterol of < 1.03 mmol/l in men and < 1.29 mmol/l in women, 4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; and 5) fasting glucose ≥ 5.6 mmol/l. According to the IDF definition (Alberti et al. 2005), an increased waist circumference (≥ 94 cm for men and ≥ 80 cm for women) and at least two of the following factors are present: 1) triglycerides > 1.7 mmol/l or specific treatment; 2) HDL-cholesterol < 1.03 mmol/l in men and < 1.29 mmol/l in women or specific treatment; 3) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension; and 4) fasting plasma glucose ≥ 5.6 mmol/l or previously diagnosed type 2 diabetes. The IDF definition has ethnic-specific values for waist circumference (Study III).

4.2.3 Whole-body impedance cardiography measurement

A commercially available ICG_{WB} monitor, CircMon B202 (CircMon, JR Medical Ltd, Tallinn, Estonia), was used to measure systemic hemodynamic parameters. The subjects were interviewed, after which they lay in a supine position for at least 15 min prior to the measurement. Alternating electrical current (30 kHz, 0.7 mA) was applied to the current electrodes (Blue sensor type R-00-S, Medicotest A/S, Olstykke, Denmark) on the distal parts of the extremities just proximal to the wrist and ankles. Heart-synchronous pulsation induced impedance variation through the main vascular trees was measured from voltage electrodes placed proximally to the current electrodes. An additional pair of electrodes was placed on the knee-joint level and the calf to measure PWV, as described in section 2.3 (Studies I–IV).

It should be noted that, in the determination of PWV, there is no universally accepted method to measure the distance travelled by the pulse and that noninvasive superficial measurement allows only an estimate (Asmar et al. 1996, Laurent et al. 2006). We measured the distance (L) between the aortic arch and popliteal artery superficially (following the regions: angulus sterni – umbilicus – inquinal region – knee joint) in 130 patients. A strong correlation between L and the patient's height (H) was established ($r=0.823$, $p=0.0001$).

The measured L values were compared to the CircMon-predicted ones (57% of the patient's height). The mean difference between the measured and predicted distances was 4.3 ± 3.4 cm. The differences correlated strongly with body mass index ($r=0.54$, $p<0.0001$), indicating that the superficial measurement of L may lead to significant errors in obese patients. Therefore, L was calculated for all the patients as 57% of the patient's height (Studies I–IV).

The CircMon software automatically calculates systemic vascular resistance (SVR) by dividing the mean blood pressure by CO. In study IV, SV and SVR were (automatically) indexed to body surface area to derive stroke volume index (SI, ml/m2) and systemic vascular resistance index (SVRI, dyn*s/cm5*m2). The time resolution of the recordings was 5 ms, and hemodynamic parameters represent the mean of recordings over 30 s.

4.2.4 Arterial tension time

The foot of the ICG_{WB} signal reflects the onset of SV-induced arterial distension in the aortic arch, whereas the peak of the ICG_{WB} signal reflects the integrated maximum distension of the arteries over the cardiac cycle. We hypothesized that, in the case of increased arterial load (increased stiffness or systemic vascular resistance or both), the capacity of the arteries to buffer the pressure changes induced by SV is reduced, thus reducing the overall distending time of the arteries from the minimum to maximum cross-sectional diameter. On the other hand, in the case of a low SV, the distending pressure of the arteries is reduced, possibly leading to a shorter distending time of the arterial wall.

The Circmon software automatically detects point A (Figure 4.1), which is defined as the beginning of a sharp upstroke of the heart related impedance. Moreover, the software automatically detects point B (Figure 4.1), which is defined as a point of the first maximum deflection of the impedance curve after the sharp upstroke. A new hemodynamic parameter, namely arterial tension time (ATT), was defined as a time interval tB – tA between moments tA and tB corresponding to the points A and B of the curve. ATT coincides with the time difference between the onset of SV-induced arterial distension and maximal integrated arterial distension.

The CircMon software automatically calculates stroke volume distribution index (SVDI), which characterises SV distribution between the central and peripheral parts of the circulation (the higher the value, the smaller part of SV will be distributed to peripheral circulation): SVDI (%) = [1/(C/D)] x 100,

where C is the duration of the cardiac cycle, and D is the duration from the peak impedance to the onset of the next cardiac cycle (Figure 4.1). C and D were manually calculated from the heart rate and SVDI, respectively. Furthermore, ATT was manually calculated by subtracting D from C (Study IV).

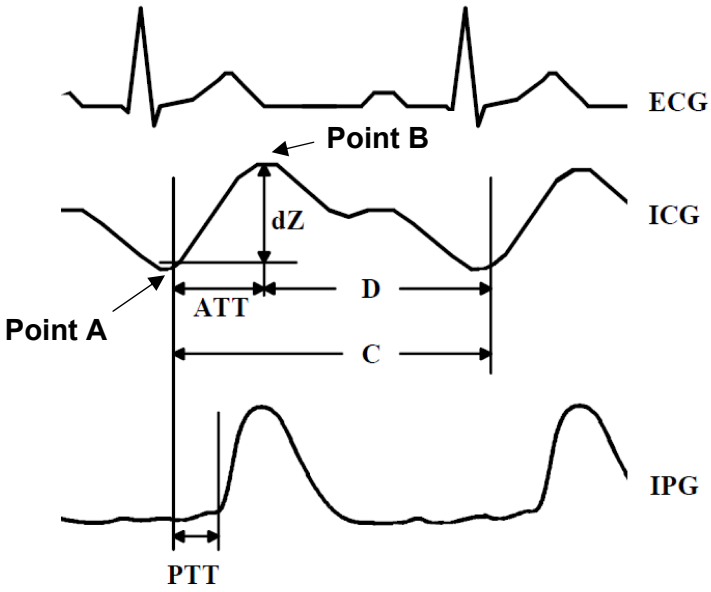

Figure 4.1: Synchronous recording of the electrocardiogram (ECG), whole-body impedance cardiogram (ICG) and impedance plethysmogram (IPG). The time difference between the feet of the ICG and IPG indicates the pulse transit time (PTT) from the aortic arch to the popliteal artery. dZ is the amplitude of heart synchronous impedance variation, C is the duration of the cardiac cycle, and D is the duration from the peak dZ to the onset of the next cardiac cycle. Arterial tension time (ATT) indicates the time interval tB – tA between moments tA and tB corresponding to the points A and B.

Adapted from Clinical Physiology and Functional Imaging, 31, Koivistoinen T, Kööbi T, Moilanen L, Jula A, Lehtimäki T, Hyttinen J, Kähönen M. Arterial tension time reflects subclinical atherosclerosis, arterial stiffness and stroke volume, 464-471, Copyright (2011) with permission from John Wiley and Sons.

The repeatability of the ATT between the two measurements was assessed (n=336). The mean difference of the two measurements was 0.6 ms (SD 16.4 ms), the coefficient of variation 14.4% and the coefficient of repeatability 32.8 ms (Bland and Altman 1986). Mean values between the two measurements were not statistically different (196.2 ms vs. 196.8 ms, p=0.481). The relationship

between cardiovascular risk factors, ultrasound variables, ICG_{WB} parameters and ATT was tested in a population of 336 subjects (Study IV).

4.2.5 Ultrasound measurements

The Health 2000 Survey

A high-resolution B-mode carotid ultrasound examination of the right carotid artery was performed according to a standardized protocol using a 7.5 MHz linear array transducer (Niiranen et al. 2007, Kettunen et al. 2011). The transducer was positioned to visualize both the far and near wall lumen-intima and media-adventitia interfaces at a single angle. A cine loop was recorded for 4–5 s and stored on super VHS tape. IMT measurements were performed off-line with the use of automated imaging processing software (PROWIN 23.1), and one reader was responsible for reading all ultrasound images. The mean IMT was measured from three digitized end-diastole images (incident with the R wave on a continuously recorded electrocardiogram). The between-visit coefficient of variation was 9.2% (Niiranen et al. 2005).

The computer programme PROWIN 23.1 was used to determine the arterial diameter over the distal 10 mm length of the common carotid artery from the peak systole and end-diastole images (Kettunen et al. 2011). Systolic and diastolic arterial diameters were calculated as the mean of three average systolic and diastolic arterial diameters, respectively. On the basis of ultrasound and concomitant brachial blood pressure measurements, Young's elastic modulus, arterial stiffness index, carotid artery distensibility, and carotid artery compliance were calculated (Studies II and IV). Selzer et al. (2001) have previously reported a between-visit coefficient of variation 11.05%–13.85% for YEM, ASI and Cdist using the similar measurement protocol.

The Cardiovascular Risk in Young Finns Study

Ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson, CA, USA) with 13.0 MHz linear array transducer (Raitakari et al. 2003, Juonala et al. 2008). The image was focused on the far wall of the left carotid artery, and a 5-second clip image was recorded and stored in digital

format on an optical disk for off-line analysis. Digitally stored scans were manually analysed by a single reader. The best-quality end-diastolic frame was selected (incident with the R wave on a continuously recorded electrocardiogram), and at least 4 measurements of the common carotid far wall were taken approximately 10 mm proximal to the bifurcation to derive mean IMT. The between-visit coefficient of variation was 6.4% (Juonala et al. 2011). To assess Cdist, the best-quality cardiac cycle was selected from the 5-second image clips (Juonala et al. 2005). The common carotid diameter at 10 mm from the carotid bifurcation was measured at least twice in end diastole and end systole, and the means of the measurements were used as the end-diastolic and end-systolic diameters. Ultrasound and concomitant brachial blood pressure measurements were used to calculate carotid artery distensibility. The between-visit coefficient of variation was 16.3% (Juonala et al. 2005) (Study II).

To determine FMD, the left brachial artery diameter was measured both at rest and during reactive hyperaemia (Juonala et al. 2004). Increased flow was induced by the inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 minutes, followed by a release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at rest and 40, 60 and 80 seconds after cuff release. The vessel diameter in scans after reactive hyperaemia was expressed as the percentage relative to the resting scan (100 percent). The greatest value between 40 to 80 seconds was used to derive the maximum FMD. All ultrasound scans were analysed by a single reader. The between-visit coefficient of variation was 26.0% (Juonala et al. 2004) (Study II).

Table 4.2 summarises the different whole-body impedance cardiography and ultrasound measurements used in each sub-study.

Table 4.2: Whole-body impedance cardiography and ultrasound measurements in different sub-studies.

Study	Whole-body impedance cardiography measurements	Ultrasound measurements
PWV reference values (Study I)	PWV	-
PWV in relation to other indices of vascular status (Study II)	PWV	FMD, IMT, Cdist
Relationship between PWV and cardiovascular risk factors (Study III)	PWV	-
Arterial tension time (Study IV)	PWV, SV, SVR, ATT	IMT, YEM, ASI, CAC

PWV, pulse wave velocity; SV, stroke volume; SVR, systemic vascular resistance; ATT, arterial tension time; FMD, brachial artery flow-mediated dilation; IMT, carotid artery intima-media thickness; Cdist, carotid artery distensibility; YEM, Young's elastic modulus; ASI, arterial stiffness index; CAC, carotid artery compliance.

4.2.6 Statistical methods

Statistical analyses were performed using SPSS for Windows (versions 13.0 and 16.0, SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered statistically significant. The skewed distribution of triglycerides (studies II–IV), C-reactive protein (CRP) (studies II–IV), insulin (studies II and IV), glucose (II), and PWV (study I) were corrected logarithmically before statistical analyses.

The T-test (comparison between two groups) or analysis of variance (ANOVA) (comparison between multiple groups) was used to compare the means of continuous variables. The Chi-square test was used to compare categorical variables. Regression analysis was used to study the relationships between cardiovascular risk factors, ultrasound variables, MetS components, MetS and PWV (studies II and III) or ATT (study IV). Adjusted mean PWV and systemic hemodynamic parameters were analysed using general linear models.

Pearson correlation coefficients were used to examine the degree of association between age, cardiovascular risk factors and PWV (studies I and III). In study IV, risk factors in the general linear model were defined as values at or above the sex-specific 80th percentile for body mass index, systolic blood pressure, diastolic blood pressure, LDL cholesterol, triglycerides, fasting insulin or fasting glucose. For low HDL cholesterol, the sex-specific 20th percentile cut-off point was used. Subjects with SI, IMT, PWV, YEM, ASI and CAC values in the extreme quartiles were classified into groups of best and worst quartiles of SI, IMT, PWV, YEM, ASI and CAC, respectively (study IV).

5 Results

5.1 PWV reference values (original publication I)

The healthy study population comprised 130 males (aged 26–75 years) and 153 females (aged 26–75 years), whereas the whole study population comprised 408 males (aged 25–75 years) and 391 females (aged 25–76 years). PWV was measured between the aortic arch and popliteal artery by a CircMon whole-body impedance cardiography device. Figure 5.1 presents PWV in relation to age in the entire population and in the healthy sub-sample.

Mean values of PWV by sex and age are shown in Table 5.1. In both populations, young males and females (age < 42 years) had lower PWV values than old males and females (aged ≥ 60 years), respectively ($p<0.001$ for both). Middle-aged males and females (aged 42–59 years) had higher PWV values than young males and females, and lower PWV values than old males and females, respectively ($p < 0.001$ for all).

Table 5.1: PWV by sex and age in a healthy population sample (n=283) and in a whole study population (n=799).

Age (years)	Male (PWV ± SD)	n	Female (PWV ± SD)	n	P *
		Healthy population sample			
26–41	7.7 ± 1.2	47	7.0 ± 1.0	71	0.002
42–59	9.1 ± 1.5	57	8.2 ± 1.6	59	0.005
60–75	10.7 ± 1.7	26	10.4 ± 2.9	23	0.712
All	8.9 ± 1.8	130	8.1 ± 2.0	153	< 0.001
		Whole study population			
25–41	7.7 ± 1.4	112	7.2 ± 1.2	122	0.001
42–59	9.7 ± 1.7	211	8.7 ± 1.6	161	< 0.001
60–76	11.6 ± 2.2	86	10.6 ± 2.9	108	0.01
All	9.6 ± 2.2	408	8.8 ± 2.4	391	< 0.001

SD, standard deviation. *comparison between males and females in a same age group.

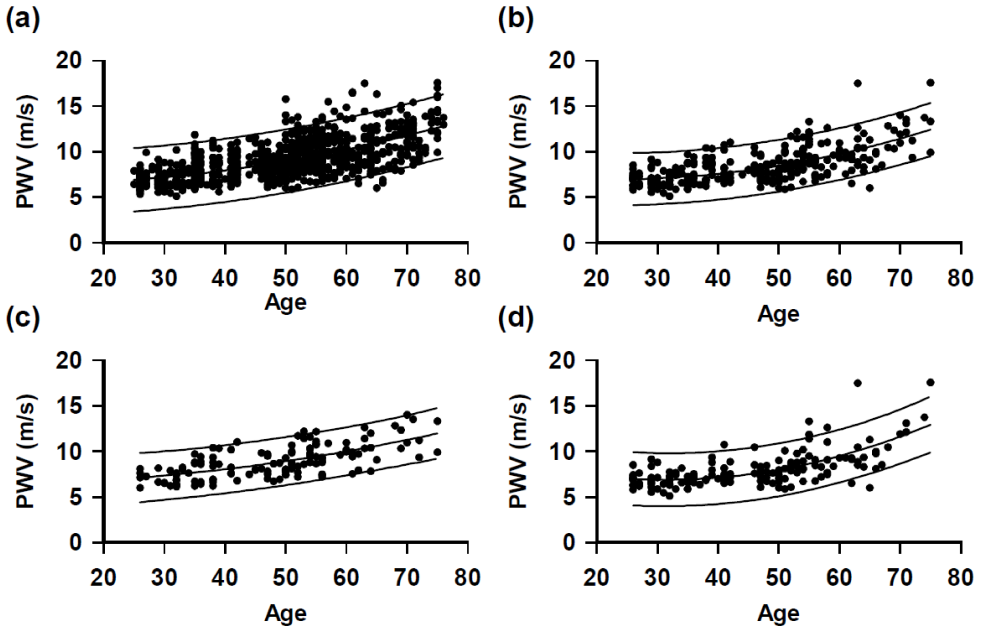

Figure 5.1: PWV in relation to age. (a) In the whole study population (n = 799). Regression equation: PWV=0.0013*(Age)²-0.0153*(Age)+6.4826. Correlation coefficient r = 0.665. (b) In subjects with no evidence of cardiovascular disease and a low burden of risk factors (n = 283). Regression equation: PWV=0.0020*(Age)²-0.0905*(Age)+7.945. Correlation coefficient r = 0.662. (c) In males with no evidence of cardiovascular disease and a low burden of risk factors (n = 130). Regression equation: PWV= 9.2790*10-4*(Age)²+0.0054*(Age)+6.3426. Correlation coefficient r =0.670. (d) In females with no evidence of cardiovascular disease and a low burden of risk factors (n = 153). Regression equation: PWV=0.0032*(Age)²-0.2036*(Age)+10.1133. Correlation coefficient r = 0.647. The central line is the standard linear regression line. The other two lines represent 2 standard deviations from the mean (95% confidence intervals).

These reference values for ICG_{WB}-based PWV in an adult Finnish population can be useful in the clinical management of patients in future studies.

5.2 PWV in relation to other indices of vascular health (original publication II)

The study cohort was divided into the three age groups (subjects aged 30–36 years, n=825, 46.7% males; subjects aged 39–45 years, n=929, 44.5% males; and subjects aged 46–76 years, n=336, 43.2% males). In subjects aged 46–76 years, carotid artery intima-media thickness (IMT), as measured by ultrasound, was directly and independently of cardiovascular risk factors associated with PWV measured by CircMon (β=1.233, p = 0.019) (Table 5.2). However, in younger subjects, IMT and PWV were not independently correlated.

Carotid artery distensibility (Cdist) was inversely and independently associated with PWV in all age groups ($p<0.04$ for all), whereas brachial artery flow-mediated dilation (FMD) and PWV were not independently related in subjects aged 30–36 years and 39–45 years (FMD data was not available for subjects aged 46–76 years) (Table 5.2).

These findings suggest that PWV reflects a different aspect of vascular damage than brachial FMD or carotid IMT in young adults, whereas the information provided by PWV and IMT in older adults as regards subclinical vascular damage may be partially similar. Moreover, the results suggest that PWV and Cdist, two independent methods for estimating arterial stiffness/distensibility, are, at least to a degree, representatives of a similar adverse process in the arterial wall.

Table 5.2: The association of PWV with IMT, FMD and Cdist for each age group.

	IMT (mm)		FMD (%)		Cdist (%/10 mmHg)	
PWV	β ± SE	p*	β ± SE	p*	β ± SE	p*
Age 30–36 years (n=825)						
Unadjusted	2.274±0.519	<0.001	-0.015±0.009	0.111	-0.443±0.061	<0.001
Age- and sex-adjusted	1.255±0.507	0.014	0.009±0.009	0.334	-0.302±0.061	<0.001
Multivariable-adjusted[a]	0.007±0.497	0.989	-0.001±0.008	0.936	-0.150±0.060	0.012
Age 39–45 years (n=929)						
Unadjusted	2.859±0.502	<0.001	-0.051±0.012	<0.001	-0.627±0.076	<0.001
Age- and sex-adjusted	1.398±0.482	0.004	-0.014±0.011	0.202	-0.411±0.074	<0.001
Multivariable-adjusted[a]	0.235±0.459	0.609	-0.014±0.010	0.167	-0.157±0.072	0.029
Age 46–76 years (n=336)						
Unadjusted	4.432±0.664	<0.001	-	-	-1.709±0.210	<0.001
Age- and sex-adjusted	2.323±0.622	<0.001	-	-	-1.065±0.196	<0.001
Multivariable-adjusted[a]	1.233±0.524	0.019	-	-	-0.359±0.173	0.038

[a]Adjusted for age, sex, systolic blood pressure, HDL cholesterol, LDL cholesterol, body mass index, triglycerides, glucose, insulin and C-reactive protein. β, unstandardized regression coefficient; SE, standard error. FMD was not measured in the Health 2000 Survey (subjects aged 46-76 years, n=336). *Between PWV and IMT, FMD or Cdist.

5.3 Cardiovascular risk factors and PWV (original publication III)

The prevalence of metabolic syndrome (MetS) according to the NCEP and IDF definitions was 41% and 47%, respectively, in men and 40% and 44%, respectively, in women. Subjects with MetS had higher PWV values than those without the syndrome (Figure 5.2). Several cardiovascular risk factors were univariately associated with PWV (Table 5.3). Systolic blood pressure, age, fasting glucose and waist circumference were independent determinants of PWV in the whole study cohort. In the healthy sub-sample population, similar findings were observed with the exception that fasting glucose was not independently associated with PWV (Table 5.4). When linear regression models also included MetS, a direct and independent association was found between MetS and PWV in both study cohorts (Table 5.5).

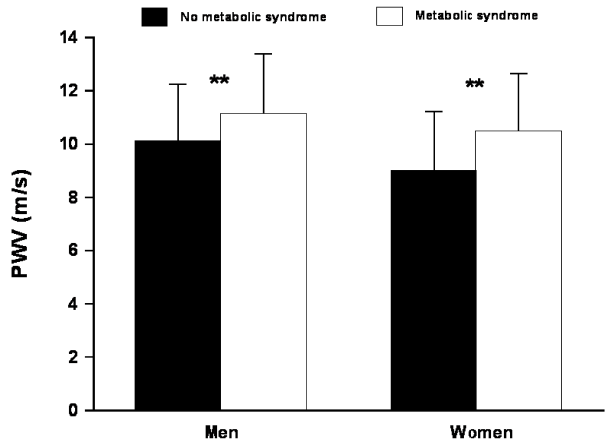

Figure 5.2: PWV (mean and standard deviation) in men and women with or without metabolic syndrome by the NCEP definition. ** $p < 0.01$.

Reprinted from Metabolism, 56, Sipilä K, Koivistoinen T, Moilanen L, Nieminen T, Reunanen A, Jula A, Salomaa V, Kaaja R, Kööbi T, Kukkonen-Harjula K, Majahalme S, Kähönen M. Metabolic syndrome and arterial stiffness: The Health 2000 Survey, 320-326, Copyright (2007) with the permission from Elsevier.

Table 5.3: Univariate correlations between cardiovascular risk factors and PWV in the whole cohort (n=393-401) and in the healthy subsample (n=197-200).

	Whole cohort		Subsample	
	r	p	r	p
Age (years)	0.510	<0.001	0.518	<0.001
BMI (kg/m^2)	0.238	<0.001	0.274	<0.001
Waist circumference (cm)	0.343	<0.001	0.353	<0.001
HDL cholesterol (mmol/l)	-0.161	0.001	-0.255	<0.001
LDL cholesterol (mmol/l)	0.062	0.217	0.208	0.003
Total cholesterol (mmol/l)	0.028	0.577	0.120	0.090
Triglycerides (mmol/l)	0.199	<0.001	0.174	0.014
Fasting glucose (mmol/l)	0.341	<0.001	0.252	<0.001
CRP (mg/l)	0.226	<0.001	0.214	0.003
Systolic blood pressure (mmHg)	0.627	<0.001	0.694	<0.001
Diastolic blood pressure (mmHg)	0.392	<0.001	0.496	<0.001
Pulse pressure (mmHg)	0.619	<0.001	0.642	<0.001
Heart rate x pulse pressure	0.627	<0.001	0.664	<0.001

Table 5.4: A linear regression model for the relationship between cardiovascular risk factors and PWV in the whole cohort (n=390) and in the healthy subsample (n=196).

	Whole cohort				Subsample		
Risk variable	β ± SE	p	R^2 change (%)	Risk variable	β ± SE	p	R^2 change (%)
SBP (mmHg)	0.05±0.00	<0.001	40	SBP (mmHg)	0.06±0.01	<0.001	48
Age (years)	0.10±0.01	<0.001	11	Age (years)	0.10±0.01	<0.001	12
Fasting glucose (mmol/l)	0.27±0.07	<0.001	3	Waist cf (cm)	0.02±0.01	0.042	1
Waist cf (cm)	0.03±0.01	<0.001	1				
R^2 (%)	55				61		

The initial stepwise regression model included age, sex, waist circumference, fasting glucose, HDL cholesterol, systolic blood pressure, CRP, triglycerides, smoking and LDL cholesterol (only in the subsample). β, regression coefficient; SE, standard error; R^2 change, change in adjusted R^2 value after addition of the respective variable in to the model; R^2, adjusted R^2 value of the whole model. SBP, systolic blood pressure; cf, circumference.

Table 5.5: A linear regression model for the relationship between metabolic syndrome (MetS), other cardiovascular risk factors and PWV in the whole cohort (n=392) and in the healthy subsample (n=197).

	Whole cohort				Subsample		
Risk variable	β ± SE	p	R^2 change (%)	Risk variable	β ± SE	p	R^2 change (%)
Age (years)	0.14±0.01	<0.001	26	Age (years)	0.13±0.02	<0.001	26
MetS (NCEP)	0.92±0.20	<0.001	4	MetS (NCEP)	0.84±0.25	<0.001	5
Sex	-0.82±0.19	<0.001	3	Sex	-0.72±0.23	0.002	2
CRP (mg/l)	0.52±0.21	0.016	0.8				
R^2 (%)	34				33		
Age (years)	0.14±0.01	<0.001	26	Age (years)	0.13±0.02	<0.001	26
Sex	-0.80±0.19	<0.001	3	MetS (IDF)	0.78±0.24	0.001	4
MetS (IDF)	0.67±0.20	0.001	3	Sex	-0.69±0.24	0.004	3
CRP (mg/l)	0.60±0.21	0.005	1				
R^2 (%)	33				33		

The initial stepwise regression model included age, sex, CRP, smoking, MetS (by NCEP or IDF definition), and LDL cholesterol (only in the subsample). β, regression coefficient; SE, standard error. R^2 change, change in adjusted R^2 value after addition of the respective variable in to the model; R^2, adjusted R^2 value of the whole model.

Tables 5.3, 5.4 and 5.5 adapted from Metabolism, 56, Sipilä K, Koivistoinen T, Moilanen L, Nieminen T, Reunanen A, Jula A, Salomaa V, Kaaja R, Kööbi T, Kukkonen-Harjula K, Majahalme S, Kähönen M. Metabolic syndrome and arterial stiffness: The Health 2000 Survey, 320-326, Copyright (2007) with the permission from Elsevier.

Thus, in this population of older adults, MetS and several other traditional cardiovascular risk factors were found to associate with increased PWV. In other words, subjects with cardiovascular risk factors had increased arterial stiffness.

5.4 Arterial tension time (original publication IV)

Arterial tension time (ATT) was defined as the time difference between the onset of the decrease in whole-body impedance and the lowest value of whole-body impedance that coincides with the time difference between the onset of

SV-induced arterial distension and maximal integrated arterial distension. The relationship between cardiovascular risk factors, ultrasound variables, whole-body impedance cardiography parameters and ATT was tested in a population of 336 subjects (aged 46–76 years, 43.2% males).

ATT was inversely associated with age, body mass index, triglycerides, insulin, glucose, systolic and diastolic blood pressure, the prevalence of diabetes and cardiovascular disease, the frequency of antihypertensive medication, heart rate, IMT, PWV, systemic vascular resistance index (SVRI), Young's elastic modulus (YEM), and arterial stiffness index (ASI) ($p<0.03$ for all). In addition, ATT was directly related to HDL cholesterol, stroke volume index (SI) and carotid artery compliance (CAC) ($p<0.006$ for all). Of cardiovascular risk factors, age ($p<0.001$), systolic blood pressure ($p=0.012$), diastolic blood pressure ($p=0.036$) and fasting glucose ($p=0.001$) were independent determinants of decreased ATT (Table 5.6).

Table 5.6: Multivariable relations between cardiovascular risk factors and ATT (n=336).

	ATT	
	β ± SE	P
Age (years)	-0.758 ± 0.207	< 0.001
Systolic blood pressure (mmHg)	-0.331 ± 0.130	0.012
Diastolic blood pressure (mmHg)	-0.537 ± 0.255	0.036
Fasting glucose (mmol/L)	-3.970 ± 1.236	0.001

The final model for stepwise linear regression analysis initially included age, body mass index, systolic and diastolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, fasting insulin, and fasting glucose.

The accumulation of cardiovascular risk factors was associated with decreased ATT (p for trend <0.001) (Figure 5.3A). Subjects with low SI or CAC and high PWV, YEM or ASI, as well as large IMT had decreased ATT when compared with subjects with high SI or CAC and low PWV, YEM or ASI, as well as small IMT ($p<0.04$ for all) (Figure 5.4B). Moreover, subjects with high SVRI (≥75th percentile) had decreased ATT when compared to those with low SVRI (≤25th percentile) (182.6 vs. 213.6 ms, respectively, $p<0.001$).

In conclusion, decreased arterial distension time was associated with increased arterial stiffness, increased subclinical atherosclerosis and decreased stroke volume.

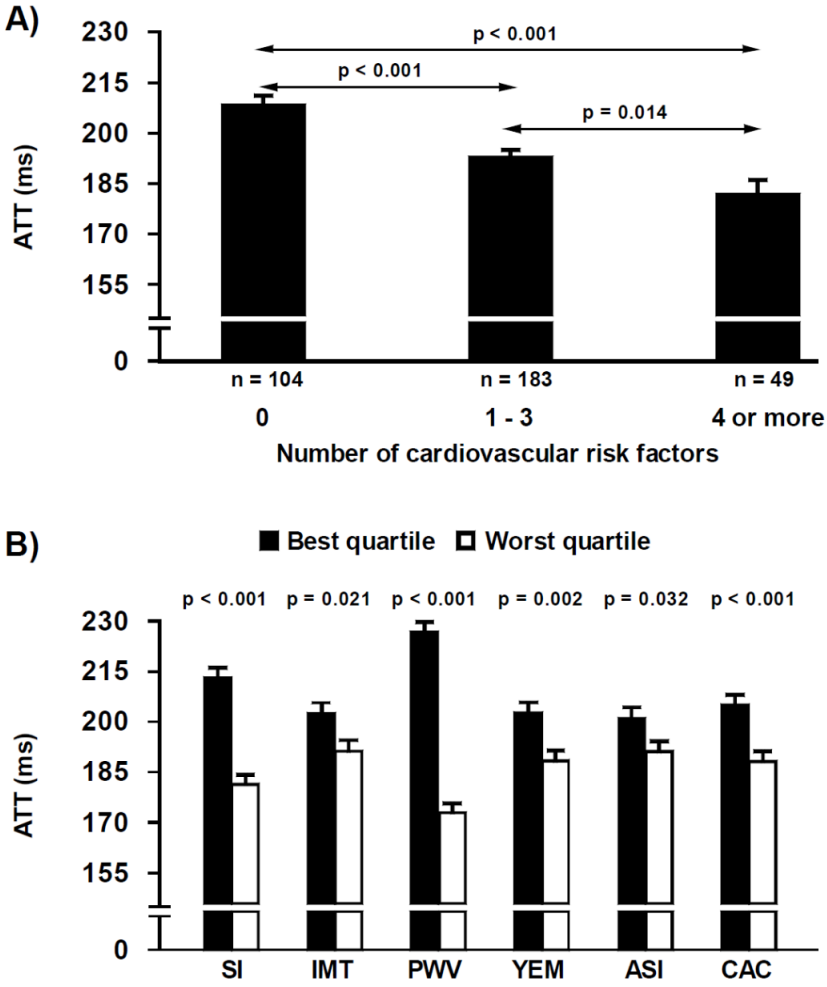

Figure 5.3: A) ATT by the number of cardiovascular risk factors. B) ATT according to the worst and best quartiles of SI, IMT, PWV, YEM, ASI and CAC. Values are expressed as age- and sex-adjusted means and standard errors. Risk factors were defined as values at or above the sex-specific 80th percentile for body mass index, systolic or diastolic blood pressure, LDL cholesterol, triglycerides, fasting insulin or fasting glucose. For low HDL cholesterol the sex-specific 20th percentile cut-off point was used.

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6 Discussion

6.1 Pulse wave velocity measured by whole-body impedance cardiography

6.1.1 Reference values

Carotid-femoral PWV has been shown to be an independent predictor of cardiovascular events and mortality in several studies (Blacher et al. 1999a, Laurent et al. 2001, Shokawa et al. 2005, Mattace-Raso et al. 2006), and it is therefore considered as the gold standard for measuring arterial stiffness (Laurent et al. 2006). However, this technique requires active participation of an experienced technician(s), in addition to being sensitive to the positioning of the transducers and time-consuming (Kööbi et al. 2003). Whole-body impedance cardiography (ICG_{WB}) could serve as a simple and operator-independent method to asses PWV, but the absence of reference values has limited its use in clinical practice. To address this gap, the present study reports reference values for PWV measured by ICG_{WB} for males and females in different age groups with no evidence of cardiovascular disease and a low burden of risk factors.

The Reference Values for Arterial Stiffness' Collaboration published reference values for carotid-femoral PWV in 2010 (Mattace-Raso et al. 2010). The mean (± 2 SD) PWV values of their study on subjects with normal blood pressure and no additional cardiovascular risk factors (n=1455, the sexes combined) were 6.5 ± 2.7 m/s (age category 30–39 years), 8.3 ± 3.8 m/s (age category 50–59 years), and 10.3 ± 4.8 m/s (age category 60–69 years). In the present study, the mean (± SD) PWV values were 7.7 ± 1.2 m/s for males and 7.0 ± 1.0 m/s for females (age category 26–41 years), 9.1 ± 1.5 m/s for males and 8.2 ± 1.6 m/s for females (age category 42–59 years), and 10.7 ± 1.7 m/s for males and 10.4 ± 2.9 m/s for females (age category 60–75). Taking into account the differences in the age categories, the reported PWV values in the present study are very similar to those observed by the Reference Values for Arterial

Stiffness' Collaboration. These reference values for ICG_{WB}-based PWV can be useful in the clinical management of patients in future studies.

Because the effects of aging and cardiovascular risk factors on the dynamic properties of the arterial tree are inhomogeneous, measuring PWV over arteries with different properties may be considered as a methodological limitation. However, the inclusion of the femoral artery in the measurement setup could be important, since it has been suggested that the deleterious effects of cardiovascular risk factors on local arterial stiffness are stronger in the more muscular than the more elastic arteries (Schram et al. 2004, Ferreira et al. 2005). Moreover, by measuring PWV from a longer distance than carotid-femoral PWV, a more global index of vascular health might be achieved.

Other potential methodological limitation is the measurement of pulse transition in the aortic arch. Due to its integrated nature (the sum of the arterial plethysmograms of the whole body), ICG_{WB} does not reflect the beginning of the pulse transition in the aortic arch precisely enough, resulting in a slight overestimation of the PWV when compared with the Doppler method (Kööbi et al. 2003). However, this small bias was corrected (Eq. 24), and corrected values were used in all studies.

6.1.2 PWV in relation to other indices of vascular health

With aging and the accumulation of cardiovascular risk factors, several adverse structural alterations occur in the arterial wall. These include a decreased elastin content, a deposition of collagen, collagen cross-links from advanced glycation end products and age-dependent intima-media thickening (Lakatta and Levy 2003, O'Rourke and Hashimoto 2007, Cecelja and Chowienczyk 2009, McEniery et al. 2009, Nichols et al. 2011). These changes have marked and progressive negative effects on the cushioning function of elastic arteries, i.e. arterial stiffness is increased (Lakatta and Levy 2003, O'Rourke and Hashimoto 2007, McEniery et al. 2009, Nichols et al. 2011). The pathophysiology of atherosclerosis involves many similar features and it has therefore been unknown whether arterial stiffening reflects the atherosclerotic process or an alternative pathology of the vascular wall (Zieman et al 2005, Cecelja and Chowienczyk 2009, Townsend et al. 2015).

Carotid artery intima-media thickness (IMT) is measured by high resolution B-mode ultrasound, and it is the most widely accepted non-invasive marker of subclinical atherosclerosis (Bruno et al. 2014). The Moens-Korteweg equation

(Eq. 14) theoretically links IMT and PWV together, although previous clinical studies on the association between PWV and carotid IMT have been inconsistent (Liang et al. 1998, van Popele et al. 2001, Oren et al. 2003, Kobayashi et al. 2004, Gomez-Marcos et al. 2011). As hypothesised in section 2.2.5, a plausible reason for these conflicting findings in clinical studies is that PWV reflects the atherosclerotic process only after a certain level. The findings in the present study support this view, since PWV was not found to associate with IMT in young adults, but in older individuals, PWV and IMT were directly and independently correlated. Further support to the view was provided by the lack of an association between PWV and FMD. In other words, our findings suggest that PWV reflects a different aspect of vascular damage than traditional indices of atherosclerosis in young adults, but in older individuals with a longer exposure to cardiovascular risk factors and presumably more advanced atherosclerosis, it partially reflects similar adverse vascular wall process. Therefore, the present findings encourage the use of a combination of complementary non-invasive methods to evaluate vascular wall alterations, particularly in young adults.

Although the Moens-Korteweg (Eq. 14) and Bramwell-Hill (Eq. 15) equations theoretically link PWV and arterial distensibility together, very few data are available to explore the relationship between these two. Previously, van Popele et al. (2001) and Liang et al. (1998) have reported an inverse (univariate) association between PWV and carotid artery distensibility (Cdist). In line with these, we found an independent (inverse) relationship between PWV and Cdist in a population of over 2000 Finnish adults. This finding suggests that, despite methodological and physiological differences, PWV and Cdist are both representatives of the same entity of vascular damage.

6.1.3 Cardiovascular risk factors and PWV

In the present study, subject with metabolic syndrome had higher PWV values compared to those without the syndrome, a finding which is in line with previous studies (Li et al. 2005, Schillaci et al. 2005, Ahluwalia et al. 2006). Cardiovascular risk factors including age, systolic blood pressure, diastolic blood pressure, body mass index, waist circumference, as well as triglyceride, HDL cholesterol, fasting plasma glucose and CRP levels correlated statistically significantly with PWV. These findings are also well in line with previously published data (Mitchell et al. 2004, Tomiyama et al. 2005). All in all, our

findings on the relationship between cardiovascular risk factors and PWV are very similar in comparison to previous studies and, therefore, the current results suggest that the whole-body impedance cardiography method can be used in the measurement of PWV in large epidemiological studies.

6.2 Arterial tension time

Although carotid IMT is the most widely accepted non-invasive marker of subclinical atherosclerosis and it has been related to cardiovascular disease and cardiovascular events, there is also scepticism towards its usefulness as a risk stratification tool for the general population (Helfand et al. 2009, Lorenz et al. 2010). One of the major concerns is the relatively modest predictive value of absolute risk (Lorenz et al. 2010, Simon et al. 2010).

Brachial artery flow-mediated dilation (FMD), a surrogate marker of endothelial function, measures nitric-oxide-dependent vasodilatation after artificially induced hypoxia. It is considered to reflect early and predominantly functional atherosclerotic changes in the arterial wall (Ter Avest et al. 2007). Impaired FMD relates to the prevalence of coronary atherosclerosis (Neunteufl et a. 1997) and has been shown to predict cardiovascular events (Chan et al. 2003). The major limitation of the FMD measurement is the lack of methodological standardization (Ghiadoni et al. 2012).

Local arterial stiffness of superficial arteries, particularly of the carotid artery, can be determined using ultrasound devices. A major advantage is that local stiffness can be directly measured from the change in pressure driving the change in volume (Laurent et al. 2006). The major limitations are the requirement of a high degree of technical expertise and longer measurement time as compared to pulse wave velocity. In addition, the use of brachial pulse pressure instead of central pulse pressure in the calculation may overestimate local stiffness (Laurent et al. 2006). Moreover, previous studies on the possible relationship between (carotid) artery elasticity indices and cardiovascular events or mortality have reported inconclusive results (Störk et al. 2004, Dijk et al. 2005, Ogawa et al. 2009).

The SV to pulse pressure ratio has been shown to associate with cardiovascular risk and cardiovascular events (de Simone et al. 1999, Lind et al. 2004, 2006), but whether SV predicts cardiovascular events has not been studied extensively.

Therefore, these indices of cardiovascular status (IMT, FMD, SV, local arterial stiffness) are widely studied and can provide various information about cardiovascular health but also include several limitations. Moreover, their ability to predict cardiovascular risk is, to a degree, limited. It could hence be of clinical interest to develop an integrated cardiovascular parameter reflecting several aspects of the cardiovascular system and thus possibly improve risk stratification.

The foot of the ICG_{WB} signal reflects the onset of arterial distension induced by stroke volume (SV) in the aortic arch, whereas the peak of the ICG_{WB} signal reflects the integrated maximum distension of arteries over the cardiac cycle. The current study introduced a new ICG_{WB}-based hemodynamic parameter, arterial tension time (ATT), which was defined as the time difference between a sharp upstroke of the heart related impedance and the first maximum deflection of the impedance curve after the sharp upstroke. ATT coincides with the time difference between the onset of SV-induced arterial distension and maximal integrated arterial distension. We hypothesised that, in the case of increased arterial load (increased stiffness or systemic vascular resistance or both), the capacity of the arteries to buffer pressure changes induced by SV is reduced, thus reducing the overall distending time of the arteries from the minimum to maximum cross-sectional diameter. On the other hand, in the case of a low SV, the distending pressure of arteries is reduced, possibly leading to a shorter distending time of the arterial wall. In support of these hypotheses, decreased ATT was found to associate with increased local and segmental arterial stiffness, increased systemic vascular resistance index and decreased stroke volume index. Moreover, the accumulation of cardiovascular risk factors and increased carotid artery intima-media thickness, as a measure of subclinical atherosclerosis, were related with decreased ATT.

Therefore, our current findings suggest that ATT could potentially include information on several aspects of cardiovascular structure and function and possibly serve as a new integrated parameter for cardiovascular risk stratification.

6.3 Clinical implications and future perspectives

In the present study, PWV was not associated with carotid IMT in young adults, but, in older individuals, PWV was directly and independently correlated with

carotid IMT. Hypertension is a strong predictor of PWV (Cecelja and Chowienczyk 2009) and we may therefore speculate that PWV might be useful in detecting early and diffuse vascular damage in young hypertensive subjects (Rubba and Agewall 2012). In contrast, carotid IMT might be accurate for early detection of atherosclerotic plaques in young hyperchlosterolaemia patients and other subjects at high cardiovascular risk (Rubba and Agewall 2012). Therefore, future studies should be conducted with a combination of complementary non-invasive methods in order to arrive at a more accurate and comprehensive understanding of vascular health, particularly in young adults.

PWV is a widely-studied measure of vascular health and a strong predictor of cardiovascular events, cardiovascular mortality and all-cause mortality (Vlachopoulos et al. 2010a). It has therefore been suggested that PWV currently fulfils the criteria of a biomarker and should be transferred from research to clinical practice (Vlachopoulos et al. 2010b, Rubba and Agewall 2012). Several different methods have been developed to measure PWV, and of these, the measurement of transit time between the carotid and femoral artery using mechanotransducers is used in most of the epidemiological studies demonstrating the predictive value of PWV for cardiovascular events. However, it should be noted that the femoral pressure waveforms may be difficult to record accurately in subjects with obesity or peripheral artery disease (Laurent et al. 2006). An ICG_{WB} method with an additional voltage sensing channel to measure PWV has previously been shown to be well in agreement with the Doppler ultrasound method (Kööbi et al. 2003). Moreover, a previous study (Tahvanainen et al. 2009) has shown good repeatability and reproducibility indexes for PWV as measured by ICG_{WB}. Furthermore, ICG_{WB} is an operator-independent and inexpensive method to measure PWV. Thus, findings in the previous (Kööbi et al. 2003, Tahvanainen et al. 2009) and in the present study suggest that ICG_{WB} is applicable for PWV measurement in large-scale epidemiological studies. Moreover, current reference values can be useful in the clinical management of patients, especially in detecting early vascular damage or an increased risk of cardiovascular complications.

The ATT developed and tested in this study could potentially include information on several aspects of the cardiovascular structure and function and thus possibly serve as a new parameter of cardiovascular health. Due to its integrated nature (the sum of the arterial plethysmograms of the whole body), ICG_{WB} is an ideal method for assessing ATT. Future longitudinal studies should address the relationship between ATT and cardiovascular disease and events.

7 Summary and conclusions

I. ICG_{WB} could serve as a simple and an operator-independent method of assessing PWV, but the absence of reference values has limited its use in clinical practice. The present study established reference values for PWV as measured by ICG_{WB} for males and females in different age groups with no evidence of cardiovascular disease and a low burden of risk factors. The reference values can be useful in the clinical management of patients in the future studies.

II. Previously, it has been unknown whether arterial stiffening reflects the atherosclerotic process or an alternative pathology of the vascular wall. The current findings suggest that PWV reflects a different aspect of vascular damage than indices of early atherosclerosis (FMD, IMT) in young adults. In contrast, in older adults with a longer exposure to cardiovascular risk factors and presumably more advanced atherosclerosis, the information provided by PWV and IMT may be, to some extent, similar. The present findings encourage the use of a combination of complementary non-invasive methods to evaluate vascular wall alterations, particularly in young adults.

III. The applicability of the ICG_{WB} method for measuring PWV in epidemiological studies has not been tested previously. The present findings on the relationship between cardiovascular risk factors and PWV are very similar when compared to previous studies and, therefore, the current results suggest that ICG_{WB} can be used in the measurement of PWV in large epidemiological studies.

IV. The present study introduced and evaluated a new hemodynamic parameter based on ICG_{WB}, namely ATT, which was defined as the time difference between the SV-induced arterial distension and maximal integrated arterial distension. ATT was found to associate with cardiovascular risk factors, as well as with indices of arterial stiffness, atherosclerosis and cardiac pump function. Therefore, ATT could potentially include information on several aspects of

cardiovascular structure and function, and possibly serve as a new parameter of cardiovascular health.

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Clin Physiol Funct Imaging (2007) **27,** pp191–196 doi: 10.1111/j.1475-097X.2007.00734.x

Pulse wave velocity reference values in healthy adults aged 26–75 years

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Summary

The stiffening of arteries is associated with various cardiovascular diseases. Arterial stiffening can be studied utilizing arterial pulse wave velocity (PWV), but the absence of reliable reference values for PWV has limited its use in clinical practice. The aim of this study was to establish a range of reference values for PWV. PWV was examined by measuring the time difference of systolic pulse waves in arteries from the aortic arch to the popliteal artery using whole-body impedance cardiography (ICG). The study population consisted of 799 individuals (age range 25–76 years), 283 of whom had no evidence of cardiovascular disease, and a low burden of risk factors was selected to represent an apparently healthy population. In healthy study population, PWV was higher in males ($8{\cdot}9 \pm 1{\cdot}8$ m s^{-1}) than females ($8{\cdot}1 \pm 2{\cdot}0$ m s^{-1}, $P<0{\cdot}001$). Young males had lower PWV values than old males. Correspondingly, young females also had lower PWV values than old females. PWV was clearly associated with age, and PWV was higher in young and middle-aged males than in females. There was no statistically significant difference between old males and females in PWV. In conclusion, whole-body ICG provides a practical method for PWV measurement. Reference values can be useful in the clinical management of patients, especially in detecting early vascular disease or an increased risk of cardiovascular complications.

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Financial support has been received from the Medical Research Fund of Tampere University Hospital and the Academy of Finland.

Accepted for publication

Received 16 August 2006;
accepted 30 January 2007

Key words

arterial compliance; arterial stiffness; Doppler ultrasound; haemodynamic parameters; impedance cardiography

Introduction

The pulsatile nature of blood flow, the complex structure of the vessel wall and the continuously changing tone of the smooth muscle component makes the study of large artery dynamics challenging. The evaluation of large artery dynamics is, however, potentially important even in routine clinical practice, since pulse pressure, pulse wave velocity (PWV) and other parameters reflecting arterial stiffness are associated with increased cardiovascular risk in several patient groups (Lehmann *et al.*, 1998; Blacher *et al.*, 1999a,b, 2000; Amar *et al.*, 2001) as well as in apparently healthy subjects (Mattace-Raso *et al.*, 2006). In patients with end-stage renal disease, essential hypertension or diabetes, increased aortic stiffness determined by aortic PWV is a strong independent predictor of coronary events as well as all-cause and mainly cardiovascular mortality (Blacher *et al.*, 1999a,b; Laurent *et al.*, 2001; Boutouyrie *et al.*, 2002; Cruickshank *et al.*, 2002). Furthermore, aortic PWV has been shown to be a strong independent marker of cardiovascular diseases and predictor of cardiovascular death in subjects aged 70–100 years (Meaume *et al.*, 2001a,b).

Pulse wave velocity measurements have been mostly carried out with methods utilizing Doppler ultrasound or mechano-electrical pulse transducers (Lehmann *et al.*, 1992; Wilkinson *et al.*, 1998). PWV can also be measured by whole-body impedance cardiography (PWV_{ICG}), which provides a handy and reliable tool for evaluating arterial stiffness simultaneously with conventional haemodynamic parameters. This operator-independent method is highly repeatable and reproducible (Kööbi *et al.*, 2003).

An easy to operate, reliable and non-invasive method for PWV measurements would be useful for screening patients with subacute or early cardiovascular disease and for subjects at an increased risk of atherosclerotic vascular disease. The absence of reference values for PWV measurements has, however, limited the use of this method for diagnosing arterial stiffness, especially

in clinical practice. The aim of the present study was to establish a range of reference values for PWV in an adult Finnish population. Reference values are presented for a healthy sample of subjects with a low burden of cardiovascular risk factors ($n = 283$), and also for a sample of subjects without any exclusion criteria ($n = 799$).

Methods

Study population

The present study population was combined from three distinct studies. The first source for the study population was a large Finnish cross-sectional health examination survey (the Health 2000 survey) carried out in 2000–2001 (Aromaa & Koskinen, 2004). Four hundred and fifty-five individuals (age range 46–76 years) participating in the supplemental study with whole-body impedance cardiography measurements in the catchment areas of Tampere and Turku University Hospitals were selected to our study group. The second source was the Cardiovascular Risk in Young Finns Study, which is an on-going multicentre follow-up study of atherosclerosis risk factors in Finnish children and young adults. The first cross-sectional survey was conducted in 1980 (Åkerblom *et al.*, 1985). In 2003–2004, we re-examined the haemodynamic parameters of 257 persons in this group, who by then had reached the age of 25–42 years. The third source for the study population was the Tampere Ambulatory Blood Pressure study, in which healthy untreated male volunteers were recruited at routine health check-ups offered for all individuals aged 35, 40 and 45 years at the Community Health Care Centre of the City of Tampere between 1987 and 1991. After a mean of 10·8 years (range 8·8–12·3), 87 (85%) subjects participated in the follow-up visit including also whole-body impedance cardiography measurement. Altogether, 799 subjects participated in these three different studies in Tampere and Turku University Hospitals and were selected to our present study.

To generate a healthy sample of subjects with a low burden of cardiovascular risk factors, participants were excluded for the following reasons: abnormal body weight (body mass index $<18{\cdot}5$ or ≥ 30 kg m^{-2}); drug treatment for hypertension; current smoking; treatment for dyslipidaemia or fasting serum total cholesterol $>6{\cdot}1$ mmol l^{-1} in subjects under 30 years of age, $>6{\cdot}9$ mmol l^{-1} in subjects aged 30–49 years and $>7{\cdot}8$ mmol l^{-1} in subjects aged 50 years or older (Rustad *et al.*, 2004); diagnosed diabetes or fasting plasma glucose $\geq 7{\cdot}0$ mmol l^{-1}; or coronary heart disease. The exclusion was based on medical history, physical examination, biochemical tests and ECG. After exclusion, 283 individuals with PWV_{ICG} data were available and these data were used to establish a range of reference values of PWV_{ICG} for an apparently healthy population (Table 1).

PWV_{ICG} measurement principles

Since fluid in arteries is incompressible, energy propagation occurs predominantly along the arterial wall and not through the blood. Arterial wall thickness and lumen diameter are thus the major determinants of PWV (Kööbi *et al.*, 1997). PWV is calculated from the measurement of pulse transit time and the distance travelled by the pulse between the two recording sites in the arterial tree.

The whole-body impedance cardiography measurements were carried out by a commercially available circulation monitor device CircMon B202 (CircMon^{TM}; JR Medical Ltd, Tallinn, Estonia), which includes two impedance cardiography channels as well as an ECG channel. A pair of electrically connected current electrodes (Blue Sensor type R-00-S; Medicotest A/S, Ölstykke, Denmark) were placed on the extremities just proximally to the wrists and the ankles. Voltage electrodes were placed proximally to the current electrodes, with a distance of 5 cm between the centres of the electrodes. The CircMon software estimates the foot of the whole-body impedance cardiogram that coincides with pulse transmission in the aortic arch. The distal impedance plethysmogram was recorded from a popliteal artery at knee joint level. The active electrode was placed on the lateral side of the knee and the reference electrode on the calf, the distance between the electrodes being roughly 20 cm (Fig. 1).

When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases, and this can be measured by the voltage-sensing electrodes on the distal parts of the extremities. The CircMon software measures the time difference between the onset of the decrease ('foot') in impedance in the whole-body impedance

Table 1 Characteristics of subjects studied.

	Healthy population sample ($n = 283$)			Whole study population ($n = 799$)		
Variable	**Male (mean ± SD)**	**Female (mean ± SD)**	***P*-value**	**Male (mean ± SD)**	**Female (mean ± SD)**	***P*-value**
Age (years)	48 ± 12	45 ± 13	0·033	50 ± 13	50 ± 14	0·816
Height (cm)	178 ± 7	165 ± 6	<0·001	178 ± 7	164 ± 6	<0·001
Weight (kg)	80 ± 10	66 ± 8	<0·001	86 ± 14	71 ± 14	<0·001
BMI	25 ± 3	24 ± 3	<0·001	27 ± 4	27 ± 5	0·110
SAP (mmHg)	126 ± 15	118 ± 17	<0·001	130 ± 18	123 ± 21	<0·001
DAP (mmHg)	73 ± 11	67 ± 12	<0·001	74 ± 12	67 ± 13	<0·001

BMI, body mass index; SAP, DAP, systolic and diastolic blood pressure.

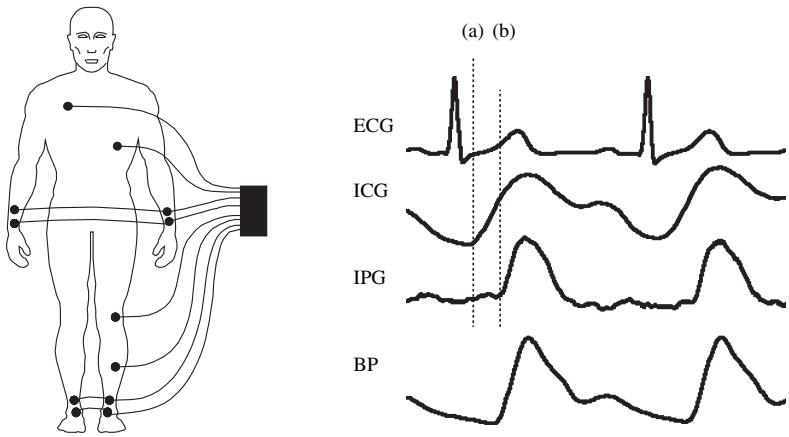

Figure 1 On the left: Placement of electrodes in whole-body impedance cardiography with an additional voltage sensing channel on the left calf for pulse wave velocity measurement. On the right: Synchronous recording of electrocardiogram (ECG), whole-body impedance cardiogram (ICG), impedance plethysmogram of popliteal artery (IPG) and blood pressure (BP). Time difference between the feet of the ICG (a) and IPG (b) indicates the pulse transit time from aortic arch to popliteal artery.

signal and, later, the popliteal artery signal (Fig. 1). By means of this time difference and the estimated distance between the electrodes, the software calculates the PWV value. The ICG method has been described in detail previously (Kööbi *et al.*, 1997).

Non-invasive superficial measurement allows only an estimate of the distance travelled by the pulse (Asmar *et al.*, 1996). We measured distance (D) between the aortic arch and popliteal artery superficially (following the regions: angulus sterni – umbilicus – inquinal region – knee joint) in 130 patients. A strong correlation between D and patient's height (H) was established ($r = 0{\cdot}823$, $P = 0{\cdot}0001$, regression equation $D = 0{\cdot}524*H + 12{\cdot}2$). Measured D values were compared with CircMon predicted ones (57% of the patient's height for adult population). Mean difference between the measured and predicted distances was $4{\cdot}3 \pm 3{\cdot}4$ cm. The differences correlated strongly with BMI ($r = 0{\cdot}54$, $P<0{\cdot}0001$) indicating that the superficial measurement of D may lead to significant errors in obese patients. Therefore, D was calculated for all the patients as 57% of patient's height.

Our previous results have shown that PWV values calculated using the whole-body impedance cardiogram systematically slightly overestimate those by the Doppler method. This small bias can be corrected using the equation: $PWV_{ICG} = 0{\cdot}696 \times PWV_{ICG} + 0{\cdot}864$, which was the case in the present study (Kööbi *et al.*, 2003). PWV_{ICG} is the PWV value measured by CircMon and PWV_{ICG} the PWV value after correction, which was used in the present study. In the previous study the proximal Doppler flow tracing at the aortic arc was recorded by placing the transducer in the suprasternal notch. The distal Doppler flow tracing was obtained from the popliteal artery by holding the probe in the popliteal fossa at knee joint level (Kööbi *et al.*, 2003). The reproducibility values of the PWV measurement are similar between the whole-body impedance cardiography and the Doppler ultrasound. A reproducibility value of $2{\cdot}42$ m s^{-1} (2 SD between two measurements) has been reported for PWV measured by whole-body impedance cardiogram and $2{\cdot}17$ m s^{-1} for PWV measured by Doppler ultrasound (Kööbi *et al.*, 2003).

Study protocol

The subjects were interviewed after which they lay in supine position for at least 15 min prior to the measurements. At that time, PWV_{ICG} electrodes were applied. The measurement of PWV_{ICG} lasted for 10 min in supine position, and arterial blood pressure was measured before and after the measurement using the standard cuff method. Venous blood samples were drawn from the antecubital vein following an overnight fast. Total serum cholesterol and plasma glucose concentrations were determined by means of routine clinical chemistry methods. The study protocol was approved by the Ethical Committee of Tampere University Hospital, and informed written consent was obtained from all subjects.

Statistics

Statistical analyses were performed using SPSS for Windows (version 13·0; SPSS Inc., Chicago, IL, USA). *T*-test analysis was employed to compare continuous variables between males and females. One-way ANOVA with Bonferroni *post hoc* test was used to compare PWV_{ICG} values in different age groups. Moreover, analysis of covariance (ANCOVA) was applied with systolic arterial pressure and body mass index as covariates. Pearson correlation coefficients were used to examine the degree of association between age and PWV_{ICG}. The skewed distribution of PWV_{ICG} was corrected logarithmically before statistical analyses.

Results

The healthy study population comprised 130 males (aged 26–75 years) and 153 females (aged 26–75 years). The mean PWV_{ICG} values in the healthy population were 8·9 ± 1·8 m s^{-1} and 8·1 ± 2·0 m s^{-1} for males and females respectively (P<0·001 in t-test and ANCOVA) (Fig. 2, Table 2). Mean PWV_{ICG} values in the entire population (n = 799) were 9·6 ± 2·2 m s^{-1} and 8·8 ± 2·4 m s^{-1} for males and females respectively (P<0·001 in t-test and ANCOVA) (Table 3).

In the healthy population, young males (age <42 years) had lower PWV values than older males (aged ≥60 years) (7·7 ± 1·2 m s^{-1} and 10·7 ± 1·7 m s^{-1} in the young and old, respectively, P<0·001 in ANOVA and ANCOVA). Young females (aged <42 years) also presented lower PWV values than older females (aged ≥60 years) (7·0 ± 1·0 m s^{-1} and 10·4 ± 2·9 m s^{-1} in the young and old, respectively, P<0·001 in ANOVA and ANCOVA).

In the healthy population, PWV_{ICG} was higher in young (age <42 years) and middle-aged (aged 42–59 years) males than in females (P = 0·002 and P = 0·005 in t-test in the young and middle-aged, respectively, and P<0·001 in ANCOVA). The difference in PWV_{ICG} between males and females aged over 59 years was significant in ANCOVA (P = 0·02) but not in t-test (P = 0·712). The correlation coefficient (r) between PWV_{ICG} and age was 0·662 in the entire healthy population (P<0·001) and 0·670 (P<0·001) for males and 0·647 (P<0·001) for females respectively.

Table 2 Pulse wave velocity (PWV, m s^{-1}) by sex and age in a healthy population sample (n = 283).

Age (years)	Male (PWV ± SD)	*n*	Female (PWV ± SD)	*n*	*P*-value
26–41	7·7 ± 1·2	47	7·0 ± 1·0	71	0·002
42–59	9·1 ± 1·5	57	8·2 ± 1·6	59	0·005
60–75	10·7 ± 1·7	26	10·4 ± 2·9	23	0·712
All	8·9 ± 1·8	130	8·1 ± 2·0	153	<0·001

Discussion

Pulse wave velocity measurements have been mostly conducted by means of methods utilizing Doppler ultrasound or mechano-electrical pulse transducers (Lehmann *et al.*, 1992; Wilkinson *et al.*, 1998). These techniques require active participation of an experienced technician in the measurement in addition to being sensitive to the positioning of the transducers and time consuming.

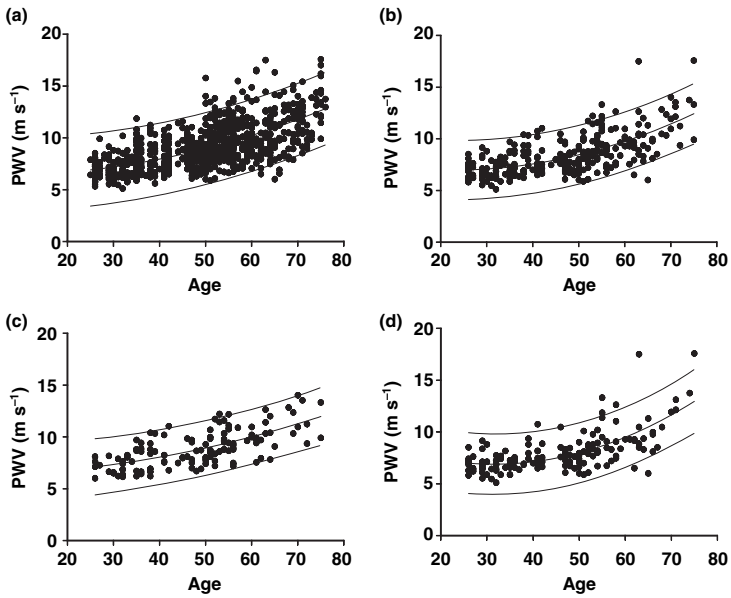

Figure 2 Whole-body impedance cardiography-derived arterial pulse wave velocity (PWV_{ICG}) in relation to age. (a) In whole study population (n = 799). Regression equation: PWV = 0·0013*$(age)^2$−0·0153*(age) + 6·4826. Correlation coefficient r = 0·665. (b) In subjects with no evidence of cardiovascular disease and a low burden of risk factors (n = 283). Regression equation: PWV = 0·0020*$(age)^2$−0·0905*(age) + 7·945. Correlation coefficient r = 0·662. (c) In males with no evidence of cardiovascular disease and a low burden of risk factors (n = 130). Regression equation: PWV = 9·2790*10^{-4}*$(age)^2$ + 0·0054*(age) + 6·3426. Correlation coefficient r = 0·670. (d) In females with no evidence of cardiovascular disease and a low burden of risk factors (n = 153). Regression equation: PWV = 0·0032*$(age)^2$−0·2036*(age) + 10·1133. Correlation coefficient r = 0·647. The central line is the standard linear regression line. The other two lines represent two standard deviations from the mean (95% confidence intervals).

Table 3 Pulse wave velocity (PWV, m s^{-1}) by sex and age in a whole study population ($n = 799$).

Age (years)	Male (PWV ± SD)	*n*	Female (PWV ± SD)	*n*	*P*-value
25–41	7·7 ± 1·4	112	7·2 ± 1·2	122	0·001
42–59	9·7 ± 1·7	211	8·7 ± 1·6	161	<0·001
60–76	11·6 ± 2·2	86	10·6 ± 2·9	108	0·01
All	9·6 ± 2·2	408	8·8 ± 2·4	391	<0·001

We have previously shown that PWV measured by whole-body impedance cardiography with complementary voltage sensing channels provides a handy, reliable, highly repeatable and reproducible means of measuring PWV simultaneously with the main haemodynamic parameters (Kööbi *et al.*, 2003). However, the absence of reference values has limited the use of this method. In the present study, we report a range of reference values for PWV measured by whole-body impedance cardiography for males and females in different age groups with no evidence of cardiovascular diseases and a low burden of risk factors. These reference values may be useful in future studies, allowing the use of a quite simple technique for the measurement of arterial dynamics. The range of reference values can also facilitate the clinical use of PWV in the risk assessment of cardiovascular diseases. As PWV has been shown to be an indicator of arterial stiffness (Asmar *et al.*, 1995; Lehmann, 1999) as well as a marker of vascular damage (Blacher *et al.*, 1999a,b; van Popele *et al.*, 2001), and as elevated PWV has been linked with cardiovascular events (Lehmann *et al.*, 1998; Blacher *et al.*, 1999a,b, 2000; Amar *et al.*, 2001), the measurement of PWV might prove useful in predicting risk and selecting subjects for early or more aggressive preventive interventions. For research purposes, a range of reference values may be helpful in patient selection for follow-up studies or intervention trials.

With increasing age, the aortic wall becomes thicker and a considerable reduction of aortic distensibility occurs. These alterations are due to a decrease in the amount, as well as the fragmentation and degeneration, of elastic tissue. The amount of collagen also increases (Lakatta *et al.*, 1987). The changes lead to increased PWV, as can also be seen from our results. The present results also showed that males had higher PWV values in the age group of <60 years, and even in those above 60 years when using BMI and systolic blood pressure as covariates. This is in accord with most of the earlier studies (Albaladejo *et al.*, 2003; Mitchell *et al.*, 2004), even though some reports suggest that PWV does not differ between the sexes (London *et al.*, 1995; Smulyan *et al.*, 2001).

Ferreira *et al.* (1999) used two pressure transducers placed on the carotid and femoral arteries and reported mean PWV values of 8·14 ± 0·14 m s^{-1} in a healthy young male population (age range 19–50 years). Kingwell *et al.* (1997) used simultaneous applanation tonometry of the carotid and femoral arteries and calculated aortofemoral PWV from these values. The mean PWV values of this study on a healthy young male population (mean age 24 ± 6 years) were 6·2 ± 0·4 m s^{-1}. In our study with a healthy young male population (age <42 years), PWV was 7·7 ± 1·2 m s^{-1} and PWV for males of all ages was 8·9 ± 1·8 m s^{-1}. Chen *et al.* (1999) and Breithaupt-Grogler *et al.* (1997) studied PWV values with a healthy aged population (mean age 64·7 ± 10·5 and 62·4 ± 7·2 years respectively) using Doppler ultrasound and sphygmographical techniques. In these studies, the mean PWV from the carotid to femoral artery using the sphygmographical technique was 9·8 ± 2·5 m s^{-1}, and aortic PWV using Doppler ultrasound 9·1 ± 2·5 m s^{-1}. In our study with a healthy middle-aged population (aged 42–59 years), PWV was 9·1 ± 1·5 m s^{-1} for males and 8·2 ± 1·6 m s^{-1} for females. In a healthy population of advanced age, PWV was 10·7 ± 1·7 m s^{-1} and 10·4 ± 2·9 m s^{-1} for males and females respectively. All in all, our present mean values of PWV_{ICG} are very similar to those observed in other studies in which varying methods of measurement have been used.

In normal arteries, there is a steep gradient of increasing arterial stiffness moving from the heart to the periphery. As the present measurement setup derives PWV from the region of the aortic arch to the popliteal artery, the PWV values measured could be somewhat higher than those usually measured by Doppler ultrasound from more central arteries. Measuring PWV over arteries with different properties may be considered as a methodological limitation. The loss of dynamic properties along the arterial tree is inhomogenous. At older age, distensibility of the muscular common femoral artery is reduced, but the distensibility of the deep and superficial muscular femoral arteries are not (Reneman *et al.*, 2005). Also, in younger populations the aortic PWV is lower than femoral PWV. However, the difference in PWV between aorta and femoral artery evens out in elderly populations (Avolio *et al.*, 1983). Furthermore, due to its integrated nature (the sum of the arterial plethysmograms of the whole body), the whole-body impedance cardiogram does not reflect the beginning of the pulse transition in the aortic arch precisely enough, resulting in a slight overestimation of the PWV when compared with the Doppler method (Kööbi *et al.*, 2003). We therefore used a correction equation to eliminate the bias between these two methods.

Pulse wave velocity can be measured using several different kinds of measurement setups. Our goal was to build up a measurement setup which makes the measurement of PWV operator-independent and as easy and fast as possible. This is beneficial in, for example, epidemiological studies. By using the knee level for PWV measurements, it is easy to locate the same positioning of the electrodes between subjects. Including the femoral artery in the PWV measurement reveals the status of arterial stiffness in the vasculature from a longer distance than most of the methods, thus providing a more global index of vascular health.

In conclusion, whole-body impedance cardiography provides a practical method for PWV measurements. A range of reference values can be useful in the clinical management of patients, especially in detecting early vascular disease or an increased risk of cardiovascular complications.

Acknowledgements

Ms Pirjo Järventausta is acknowledged for her skilful technical assistance.

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Atherosclerosis 220 (2012) 387–393

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Arterial pulse wave velocity in relation to carotid intima-media thickness, brachial flow-mediated dilation and carotid artery distensibility: The Cardiovascular Risk in Young Finns Study and the Health 2000 Survey

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ARTICLE INFO

Article history:
Received 23 March 2011
Received in revised form 11 July 2011
Accepted 1 August 2011
Available online 10 August 2011

Keywords:
Arterial stiffness
Atherosclerosis
Carotid artery
Endothelium

ABSTRACT

Objective: Increased arterial pulse wave velocity (PWV) is a strong predictor of cardiovascular events and mortality. The data regarding the relationships between PWV and other indices of vascular damage is limited and partly controversial. We conducted the present study to examine PWV in relation to non-invasive measures of early atherosclerosis (brachial flow-mediated dilation [FMD], carotid intima-media thickness [IMT]) and local arterial stiffness (carotid artery distensibility [Cdist]).
Methods: The study population consisted of 1754 young adults (aged 30–45 years, 45.5% males) participating in the Cardiovascular Risk in Young Finns Study (YFS), and of 336 older adults (aged 46–76 years, 43.2% males) participating in the Health 2000 Survey. FMD was measured only in the YFS cohort. FMD, IMT and Cdist were assessed by ultrasound, and PWV was measured using the whole-body impedance cardiography device.
Results: In young adults, FMD and IMT were not associated with PWV independently of cardiovascular risk factors. Moreover, FMD status was not found to modulate the association between cardiovascular risk factors and PWV. In older adults, PWV and IMT were directly and independently associated ($\beta = 1.233$, $p = 0.019$). In both cohorts, PWV was inversely related with Cdist, and this relation remained significant ($p < 0.04$) in models adjusted for cardiovascular risk factors.
Conclusions: The current findings suggest that PWV reflects a different aspect of vascular damage than FMD or IMT in young adults, whereas in older adults the information provided by PWV and IMT may be, to some extent, similar as regards subclinical vascular damage. The present observations also suggest that PWV and Cdist represent, at least in part, a similar adverse vascular wall process.

1. Introduction

Arterial pulse wave velocity (PWV) is a commonly used measure of arterial stiffness and a marker of vascular damage [1]. Increased PWV correlates with cardiovascular risk factors [2,3] and predicts cardiovascular events and all-cause mortality [4]. Additionally, other non-invasive methods – such as the measurement of brachial artery flow-mediated dilation (FMD), carotid artery distensibility (Cdist) and carotid artery intima-media thickness (IMT) – are widely used to assess functional and structural vascular damage [5–7].

Brachial FMD, as a surrogate marker of endothelial function, reflects early and predominantly functional changes in the arterial wall, whereas carotid IMT represents a marker of more advanced structural changes [5]. We [8] and others [9,10] have previously shown that brachial FMD and carotid IMT are inversely related,

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doi:10.1016/j.atherosclerosis.2011.08.007

suggesting that both are representatives of the same atherosclerotic process. Moreover, we have previously shown that the status of the brachial endothelial function may modify the association between cardiovascular risk factors and carotid IMT [8]. However, findings with respect to relationships between PWV and brachial FMD or carotid IMT have been inconsistent [11–18]. It therefore remains unclear whether segmental arterial stiffening, at least in its early stages, reflects the atherosclerotic process or an alternative pathology of the arterial wall [19,20]. Furthermore, although PWV and Cdist, as measures of segmental and local arterial stiffness, are often used interchangeably, the relationships between PWV and Cdist have received little interest to date.

The objective of the present study was to gain more insight into the associations of PWV with the markers of subclinical atherosclerosis (brachial FMD, carotid IMT) and local arterial stiffness (Cdist). In addition, we studied whether the status of the brachial endothelial function modifies the relationship between cardiovascular risk factors and PWV. The analyses were based on 1754 subjects from the Cardiovascular Risk in Young Finns Study (YFS) and 336 subjects from the Health 2000 Survey.

2. Methods

2.1. Subjects

The YFS is an on-going, five-centre follow-up study of atherosclerosis risk factors in Finnish children and young adults. The first cross-sectional survey was conducted in 1980 including 3596 randomly selected participants aged 3, 6, 9, 12, 15, and 18 years [21]. The latest follow-up study was conducted in 2007, with 1872 subjects (aged 30, 33, 36, 39, 42, and 45 years) attending the PWV measurement. After excluding subjects with incomplete brachial or carotid ultrasound data ($n = 23$) and those with incomplete cardiovascular risk factor data ($n = 72$) as well as female subjects who were pregnant ($n = 23$), a total of 1754 subjects comprised the first study cohort in the present analysis. Of these, 123 subjects (7.0%) were on antihypertensive, 19 (1.1%) on anti-diabetic and 38 (2.2%) on lipid-lowering medication.

The Health 2000 Survey was carried out in 2000–2001, and the overall study cohort was a two-stage stratified cluster sample (8028 subjects) representing the entire Finnish population aged 30 years and older [22]. To study cardiovascular disease more thoroughly, a supplemental study (1867 subjects, participation rate 82%) was carried out in the catchment areas of the five Finnish university hospitals. In the supplemental study, 350 subjects (aged 46–76 years) participated in carotid ultrasound and PWV examinations in the catchment areas of Tampere and Turku University Hospitals. A total of 336 subjects had complete cardiovascular risk factor data available, thus comprising the second study cohort for this analysis. Twenty-five subjects (7.4%) had self-reported cerebrovascular disease, coronary heart disease or a history of myocardial infarction. This information was not verified from the patient records. Ninety-four subjects (28.0%) were on antihypertensive, 13 (3.9%) on anti-diabetic and 32 (9.5%) on lipid-lowering medication. Informed written consent was obtained from all subjects and the studies were approved by local ethics committees.

2.2. Clinical characteristics and biochemical analyses

Height and weight were measured, and body mass index (BMI, kg/m^2) was calculated. Blood pressure was measured with a random-zero sphygmomanometer in the YFS cohort and with an automatic Omron model HEM-722C (Omron Matsuka Co., Japan) in the supplemental cardiovascular study of the Health 2000 Survey cohort. The average of three measurements was used in the analysis. Smoking behaviour was assessed with a questionnaire, and smokers were defined as those smoking on a daily basis. Venous blood samples were collected after a 12-h fast. In both cohorts, standard methods were used for high-density lipoprotein (HDL) cholesterol, triglycerides, insulin, glucose, and C-reactive protein (CRP) measurements. Details of all of the methods have been described previously [23–26]. Low-density lipoprotein (LDL) cholesterol concentration was calculated with the Friedewald formula.

2.3. Measurement of PWV

In both study cohorts, a whole-body impedance cardiography device (CircMon, JR Medical Ltd, Tallinn, Estonia) was used to determine PWV. CircMon includes a whole-body impedance cardiography channel, a distal impedance plethysmogram channel, and an ECG (electrocardiogram) channel. When the pulse pressure wave enters the aortic arch and the aorta's diameter increases, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in the whole-body impedance signal and, subsequently, in the distal plethysmogram signal from a popliteal artery at knee joint level. By means of time difference and distance between the 2 recording sites, the software calculates the PWV. The measurement is triggered by the R wave of the ECG. A more detailed description of the method [2,27], reference values [28], good repeatability and reproducibility indexes (99% and 87%, respectively) [29], and the validation study [27] have been published previously.

2.4. Ultrasound imaging

In both study cohorts, high-resolution B-mode ultrasound examinations of the carotid artery were performed according to standardised protocols [30–33]. In the YFS cohort, at least four measurements were taken to derive the mean IMT of the left carotid artery. In the Health 2000 Survey cohort, three measurements were taken to derive the mean IMT of the right carotid artery. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the carotid artery distensibility: $\text{Cdist}\ (\%/10\,\text{mmHg}) = [(D_s - D_d)/D_d]/(P_s - P_d)$, where D_s is the systolic diameter, D_d is the diastolic diameter, P_s is systolic blood pressure and P_d is diastolic blood pressure [33,34]. To asses brachial FMD, the left brachial artery diameter was measured both at rest and during the reactive hyperemia induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 min, followed by release [8]. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to the resting scan. Brachial FMD was measured only in the YFS cohort. We encourage readers to view the Supplementary Data for a more comprehensive description of ultrasound methods.

2.5. Statistical methods

In order to find out whether a possible association between PWV and ultrasound variables becomes more evident with advancing age, the YFS cohort was divided into the two age groups (subjects aged 30–36 years, $n = 825$, 46.7% males; and subjects aged 39–45 years, $n = 929$, 44.5% males). Comparison of characteristics between age groups was performed using analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables. In group comparisons, the differences between men and women were studied using t-test. The bivariate relations between cardiovascular risk factors and PWV, as well as the bivariate relations between ultrasound variables and PWV, were examined by means of linear regression analysis. Multivariable linear regression models – including age, sex, cardiovascular risk factors (systolic blood pres-

Table 1
Characteristics of the study subjects.

	Age 30–36 years (n = 825)	Age 39–45 years (n = 929)	Age 46–76 years (n = 336)	p for trend
Male subjects (%)	46.7	44.5	43.2	0.476
Body mass index (kg/m^2)	25.4 ± 4.7	26.5 ± 4.7[a]	27.0 ± 4.2[b]	<0.001
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.3 ± 0.3	1.6 ± 0.4[b,c]	<0.001
LDL cholesterol (mmol/L)	3.0 ± 0.8	3.2 ± 0.8[a]	3.4 ± 0.9[b,c]	<0.001
Triglycerides (mmol/L)	1.1 (0.8–1.5)	1.2 (0.9–1.7)[a]	1.2 (0.9–1.6)[b]	0.006
Systolic blood pressure (mmHg)	118.7 ± 13.1	122.0 ± 15.1[a]	133.9 ± 19.7[b,c]	<0.001
Diastolic blood pressure (mmHg)	73.9 ± 10.6	77.2 ± 11.5[a]	82.3 ± 9.6[b,c]	<0.001
Insulin (mmol/L)	6.6 (4.3–10.5)	6.8 (4.2–11.1)	7.5 (5.3–10.1)[b,c]	0.022
Glucose (mmol/L)	5.2 (4.9–5.5)	5.4 (5.0–5.7)[a]	5.7 (5.2–6.0)[b,c]	<0.001
C-reactive protein (mg/L)	0.8 (0.4–1.7)	0.9 (0.4–1.9)[a]	1.6 (0.8–3.3)[b,c]	<0.001
Smoking prevalence (%)	19.8	18.4	22.3	0.296
Antihypertensive medication (%)	3.2	10.4[a]	28[b,c]	<0.001
Lipid-lowering medication (%)	0.6	3.6[a]	9.5[b,c]	<0.001
Anti-diabetic medication (%)	1.0	1.2	3.9[b,c]	0.001

Values are mean ± standard deviation or geometric mean (25th to 75th percentile) or percentages of subjects.
[a] p < 0.05 in pairwise comparison between subjects aged 30–36 years and subjects aged 39–45 years.
[b] p < 0.05 in pairwise comparison between subjects aged 30–36 years and subjects aged 46–76 years.
[c] p < 0.05 in pairwise comparison between subjects aged 39–45 years and subjects aged 46–76 years.

sure, HDL cholesterol, LDL cholesterol BMI, triglycerides, glucose, insulin, and CRP) and ultrasound variables (IMT, FMD or Cdist) – were constructed to study the independent associations of IMT, FMD or Cdist with PWV.

To study how the status of brachial endothelial function modifies the association between cardiovascular risk factors and PWV, FMD was categorised. Subjects with FMD values in the extreme age- and sex-specific quartiles were classified into groups of low (n = 436, FMD = 3.8 ± 2.0% [mean ± SD]) and high (n = 436, FMD = 14.8 ± 3.5%) FMD, respectively. Values between the 25th and 75th percentile were considered intermediate (n = 882, FMD = 8.7 ± 2.0%). Correlation between risk factors and PWV in each FMD group was analysed using general linear models. In the general linear model, risk factors were defined as values at or above the age- and sex-specific 80th percentile for BMI, LDL cholesterol, systolic blood pressure or fasting insulin. For low HDL cholesterol, the age- and sex-specific 20th percentile cut-off point was used. Smoking was defined as a risk factor if the subject was smoking on a daily basis.

In both study cohorts, the skewed distributions of insulin, glucose, triglycerides and CRP were corrected logarithmically before analysis. All statistical analyses were performed with SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). A 2-tailed p value of <0.05 was considered statistically significant.

3. Results

The characteristics of the study subjects are shown in Table 1. There was an overall tendency towards a deteriorating trend in various cardiovascular risk factors with the advancing age. Moreover, the frequency of antihypertensive, lipid-lowering and anti-diabetic medications increased with the advancing age (p for trend <0.002 for all). PWV was directly associated with male sex, BMI, LDL cholesterol (only in subjects aged 30–36 years and 39–45 years), triglycerides, systolic and diastolic blood pressure, as well as fasting insulin, fasting glucose and CRP; and inversely with HDL cholesterol (p < 0.003 for all) (data not shown). In addition, PWV was directly associated with the frequency of antihypertensive medication, lipid-lowering medication (only in subjects aged 39–45 years and 46–76 years) and anti-diabetic medication (only in subjects aged 30–36 years and 46–76 years) (p < 0.05 for all) (data not shown).

Men had significantly lower Cdist and higher PWV and carotid artery diastolic diameter, compared to women in all age groups (p < 0.03 for all) (Table 2). Men had higher IMT in subjects aged 30–36 years and 39–45 years (p < 0.001 for both), but there was no significant difference in IMT between men and women in subjects aged 46–76 years (p = 0.281). Men had significantly lower FMD compared to women in subjects aged 30–36 years and 39–45 years (p < 0.001 for both). For both sexes there was an increasing trend for PWV and IMT, as well as a decreasing trend for Cdist, with advancing age (p < 0.001 for all). Moreover, subjects aged 46–76 years had higher carotid artery diastolic diameter when compared to subjects aged 30–36 years (p < 0.001 for both sexes) and 39–45 years (p < 0.001 for both sexes). There was no statistically significant difference in FMD between subjects aged 30–36 years and 39–45 years (p = 0.344 for men, p = 0.234 for women).

In subjects aged 30–36 years (n = 825) and 39–45 years (n = 929), IMT was directly associated with PWV when the multivariable linear regression model additionally included age and sex (p < 0.02 for both), but after adding other cardiovascular risk factors in the model, the association between PWV and IMT was lost (p = 0.989 and p = 0.609, respectively) (Table 3). In subjects aged 46–76 years (n = 336), IMT was directly and independently associated with PWV

Table 2
Mean values of PWV, IMT, FMD, Cdist and carotid artery diastolic diameter for each age group.

	Age 30–36 years		Age 39–45 years		Age 46–76 years	
	Men (n = 385)	Women (n = 440)	Men (n = 413)	Women (n = 516)	Men (n = 145)	Women (n = 191)
PWV (m/s)	8.2 ± 1.3	7.4 ± 1.1	9.2 ± 1.6	8.0 ± 1.3	10.5 ± 2.2	9.6 ± 2.2
IMT (mm)	0.61 ± 0.09	0.59 ± 0.07	0.68 ± 0.11	0.64 ± 0.09	0.83 ± 0.17	0.81 ± 0.18
FMD (%)	7.8 ± 4.0	10.3 ± 5.1	7.5 ± 3.6	9.9 ± 4.7	–	–
Cdist (%/10 mmHg)	1.9 ± 0.6	2.2 ± 0.7	1.6 ± 0.6	1.9 ± 0.7	0.8 ± 0.4	1.0 ± 0.6
Carotid artery diastolic diameter (mm)	5.9 ± 0.5	5.3 ± 0.4	6.0 ± 0.5	5.3 ± 0.4	8.0 ± 1.0	7.2 ± 0.8

Values are mean ± standard deviation. All comparisons between men and women p < 0.03 (t test), except for IMT in subjects aged 46–76 years (p = 0.281). All comparisons between age groups p < 0.001 (t test), except for FMD (p = 0.234 for women, p = 0.344 for men) and carotid artery diastolic diameter between subjects aged 30–36 years and subjects aged 39–45 years (p = 0.931 for women, p = 0.481 for men). Abbreviations are as defined in text.

Table 3
The association of PWV with IMT, FMD and Cdist for each age group.

	IMT (mm)		FMD (%)		Cdist (%/10 mmHg)	
	$\beta \pm$ SE	p	$\beta \pm$ SE	p	$\beta \pm$ SE	p
PWV						
Age 30–36 years (n = 825)						
Unadjusted	2.274 ± 0.519	<0.001	−0.015 ± 0.009	0.111	−0.443 ± 0.061	<0.001
Age and sex-adjusted	1.255 ± 0.507	0.014	0.009 ± 0.009	0.334	−0.302 ± 0.061	<0.001
Multivariable-adjusted[a]	0.007 ± 0.497	0.989	−0.001 ± 0.008	0.936	−0.150 ± 0.060	0.012
Age 39–45 years (n = 929)						
Unadjusted	2.859 ± 0.502	<0.001	−0.051 ± 0.012	<0.001	−0.627 ± 0.076	<0.001
Age and sex-adjusted	1.398 ± 0.482	0.004	−0.014 ± 0.011	0.202	−0.411 ± 0.074	<0.001
Multivariable-adjusted[a]	0.235 ± 0.459	0.609	−0.014 ± 0.010	0.167	−0.157 ± 0.072	0.029
Age 46–76 years (n = 336)						
Unadjusted	4.432 ± 0.664	<0.001	–	–	−1.709 ± 0.210	<0.001
Age and sex-adjusted	2.323 ± 0.622	<0.001	–	–	−1.065 ± 0.196	<0.001
Multivariable-adjusted[a]	1.233 ± 0.524	0.019	–	–	−0.359 ± 0.173	0.038

[a] Adjusted for age, sex, systolic blood pressure, HDL cholesterol, LDL cholesterol, body mass index, triglycerides (log), glucose (log), insulin (log) and C-reactive protein (log). β, unstandardised regression coefficient; SE, standard error; other abbreviations are as defined in text. FMD was not measured in the Health 2000 Survey (subjects aged 46–76 years, n = 336).

in the multivariable analysis (β = 1.233, p = 0.019) (Table 3). In subjects with low FMD (n = 436), as well as in subjects with high FMD (n = 436), PWV was associated with carotid IMT when multivariable linear regression model additionally included age and sex (low FMD, 1.565 ± 0.707 [$\beta \pm$ SE], p = 0.027; high FMD, 1.564 ± 0.774, p = 0.044), but after adding other cardiovascular risk factors in the model, the association between PWV and carotid IMT was lost (p > 0.610 for both FMD groups). In all age groups, Cdist was inversely and independently associated with PWV in the multivariable analysis (p < 0.04 for all) (Table 3). All multivariable linear regression analyses were repeated after adding antihypertensive, lipid-lowering and anti-diabetic medications as dichotomous variables (additionally to other cardiovascular risk factors) in the models, producing essentially similar results (data not shown).

In subjects aged 39–45 years, FMD was inversely associated with PWV in the univariate regression analysis (β = −0.051, p < 0.001), but this relation was lost after adjustment for age and sex (p = 0.202) (Table 3). In subjects aged 30–36 years, FMD and PWV were not significantly correlated in the univariate analysis (p = 0.111). The correlation between cardiovascular risk factors and PWV across the FMD groups is shown in Fig. 1. There was an increasing trend for PWV with the accumulation of cardiovascular risk factors in all FMD groups (p < 0.001 for all).

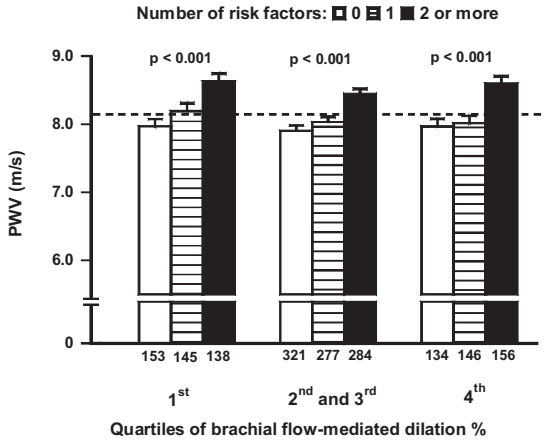

Fig. 1. Association between cardiovascular risk factors and pulse wave velocity (PWV) in young adults (aged 30–45 years, n = 1754) according to age- and sex-specific quartiles of brachial flow-mediated dilation. Risk factors were defined as values at or above the age- and sex-specific 80th percentile for BMI, LDL cholesterol, systolic blood pressure or fasting insulin. For low HDL cholesterol, the age- and sex-specific 20th percentile cut-off point was used. Smoking was defined as a risk factor if the subject was smoking on a daily basis. Dashed line represents mean for PWV. The number of subjects is shown under the columns.

4. Discussion

In this large-scale study with data from 2 cohorts, we found that PWV is not associated with brachial FMD or carotid IMT in young adults; but in older individuals PWV is directly and independently correlated with carotid IMT. Our observations therefore suggest that PWV reflects a different aspect of vascular damage than brachial FMD or carotid IMT in young adults, whereas the information provided by PWV and IMT in older adults, as regards subclinical vascular damage, may be partially similar. Furthermore, the relationship between PWV and Cdist observed in both study cohorts suggests that these two independent methods for estimating arterial stiffness are, at least to a degree, representatives of a similar adverse process in the vascular wall.

The vascular endothelium senses changes in haemodynamic signals and responds by releasing several vasoactive substances [35], and of these, nitric oxide (NO) has an important role in protecting against the early atherosclerotic changes in the vascular wall [36]. Brachial FMD, as a surrogate marker of endothelial function, measures NO-dependent vasodilatation after artificially induced hypoxemia, thus reflecting local NO bioavailability in the endothelium [36]. Hence, brachial FMD is considered as a representative of early and predominantly functional atherosclerotic changes in the arterial wall [5]. Impaired brachial FMD relates to the prevalence of coronary atherosclerosis [37] and has been shown to predict cardiovascular events [38]. The possible relationship between PWV and brachial FMD has been previously examined only in a few relatively small-scale studies, with inconclusive results. Soltész et al. [15] and Kobayashi et al. [13] reported a negative correlation between FMD and PWV (n = 101 and n = 89, respectively), whereas Nigam et al. [16] and Liang et al. [17] could not demonstrate such a relation (n = 32 and n = 30, respectively). In the present study, brachial FMD was not independently associated with PWV in the population of 1754 young adults. Moreover, the status of brachial endothelial function was not found to modify the association between cardiovascular risk factors and PWV. Therefore, the findings of the present study suggest that brachial FMD and PWV appear to represent a clearly different entity of vascular damage in young adults.

In contrast to brachial FMD, carotid IMT is considered to reflect more advanced structural atherosclerotic changes in the arterial wall [5]. Increased carotid IMT is associated with cardiovascular risk factors [30,32] and the extent of coronary artery disease [39], and has been shown to predict cardiovascular events [40]. Several previous studies have addressed the interrelationship between PWV and carotid IMT among older subjects, but the results have been inconsistent. van Popele et al. [12], Mackey et al. [41] and Kobayashi et al. [13] have shown that PWV and carotid IMT are directly associated with each other, whereas Zureik et al. [14] demonstrated that PWV is related with carotid plaques, but not with carotid IMT. In the current study, PWV and carotid IMT were directly and independently associated in a population of 336 older adults. However, in a population of >1700 young adults PWV and carotid IMT were not found to be related, thus confirming the observation from a previous study by Oren et al. [11] with a population of 524 young adults. Moreover, the status of brachial endothelial function was not found to modify the relationship between PWV and carotid IMT in young adults. Therefore, the current results suggest that PWV and carotid IMT reflect a different aspect of vascular damage in young adults, but in older adults with longer exposure to cardiovascular risk factors and presumably more advanced atherosclerosis, they partially reflect similar adverse vascular wall process.

The pathophysiology of increased PWV is a complex process including several adverse structural and functional alterations in the vascular wall. Aging and/or exposure to cardiovascular risk factors leads to an overproduction of collagen, diminished quantities of elastin, unorganised and dysfunctional fiber distribution, an infiltration of vascular smooth muscle cells into the intima, and elevated smooth muscle tone [6,19,20]. Since the pathophysiology of atherosclerosis entails similar adverse changes, and because arterial stiffening and atherosclerosis are frequently found in parallel to each other, the causality between arterial stiffening and atherosclerosis has not been fully elaborated [19]. Our findings in young adults with no clinical cardiovascular diseases and a very low prevalence of medications showed that PWV is not associated with markers of early atherosclerosis independently of cardiovascular risk factors. This observation therefore clearly provides further insight into the relationship between arterial stiffness and early atherosclerosis, particularly in young adults.

To date, the measurement of PWV is generally accepted as the most simple and robust method to estimate arterial stiffness [1]. Arterial stiffness can also be determined locally by measuring carotid artery distensibility (a change in arterial diameter for a given change in pressure). Although carotid artery distensibility and PWV are often used interchangeably, their physical definitions are not identical [7,42]. Carotid artery distensibility is a parameter that can be quantified and has units of measurement, whereas PWV provides an indirect measure of a change in the mechanical properties of a vessel segment [42]. In the present study, consistently with previous reports on an inverse (univariate) correlation between PWV and carotid artery distensibility [12,17], we found an independent (inverse) association between PWV and Cdist in both study cohorts. These data thus suggests that, despite methodological and physiological differences, PWV and Cdist are both representatives of partially the same entity of vascular damage.

Currently several different non-invasive methods have been applied for the assessment of central and peripheral PWV. Carotid-femoral PWV is considered as the gold-standard for assessing central (aortic) arterial stiffness [1] Carotid-femoral PWV has shown to be an independent predictor of cardiovascular events and mortality in several populations [1,4]. However, because carotid-femoral PWV is measured between two peripheral sites, it is not a direct measurement of aortic stiffness [43]. A more accurate assessment of aortic PWV can be achieved by measuring pulse transit time between left subclavian artery and bifurcation of abdominal aorta using continuous Doppler probes [1,44]. Although aortic PWV has shown to predict mortality in diabetic patients [44], whether it has any specific advantage compared to carotid-femoral PWV, is unclear [1]. Segmental peripheral arterial stiffness can be evaluated by measuring carotid-radial artery (brachial) PWV or femoral-posterior tibial artery (femorotibial) PWV [45]. However, these have no prognostic value for cardiovascular mortality in end-stage renal disease patients [45]. Japanese researchers have introduced brachial-ankle PWV, which reflects central elastic arterial stiffness and also peripheral muscular arterial stiffness [1,46]. Brachial-ankle PWV is independently associated with carotid-femoral PWV [46], and has shown to predict cardiovascular events and mortality in small cohorts [47,48]. In the present study we measured PWV between aortic arch and popliteal artery. We consider that including femoral artery region in the measurement of PWV is important, because especially the lower limb arteries are altered by atherosclerosis [1]. Moreover, it has been previously suggested that deleterious effects of cardiovascular risk factors on local arterial stiffness are stronger in the more muscular than the more elastic arteries [49,50].

Several limitations to the present study should be noted. Firstly, brachial FMD data was not available in the Health 2000 Survey cohort, and we were thus not able to study the relationship between PWV and brachial FMD in older subjects. Secondly, the number of the subjects in the third age group was relatively modest compared to the other two age groups. Moreover, the age range in the third age group was 30 years, whereas in the first and the second age groups it was only 6 years. Thirdly, carotid artery distensibility was calculated using brachial artery pulse pressure, which might overestimate the pulse pressure in carotid artery [1]. Fourthly, we examined the relation between PWV and other indices of vascular damage in cross-sectional settings, which cannot prove the causality between these variables. Fifthly, although PWV values measured by CircMon are highly comparable to those measured by Doppler ultrasound [27], the current method of measuring PWV remains to be adopted on a wider scale in epidemiological settings, which constitutes an apparent limitation in regard to the comparability of the present findings with observations from other cohorts. Finally, the Health 2000 Survey and the YFS were independent studies carried out in 2000–2001 and 2007, respectively. Mean carotid IMT, mean end-systolic diameter and mean end-diastolic diameter were measured from the left carotid artery in the YFS cohort, and from the right carotid artery in the Health 2000 Survey. Moreover, in the YFS ultrasound studies were performed using a 13.0 MHz linear array transducer, whereas in the Health 2000 Survey we used 7.5 MHz linear array transducer. Thus, these differences in measurement methods constitute a potential limitation in regard to the comparability of the current findings between young and older adults. However, we believe that the 13.0 MHz and 7.5 MHz linear probes are interchangeable in imaging common carotid artery because it is located close to the skin. Moreover, de Freitas et al. [51] have previously shown that aging contributes similarly to IMT of the left and right carotid arteries.

In conclusion, the present findings suggest that PWV in young adulthood reflects a different aspect of subclinical vascular damage than brachial FMD or carotid IMT, while in older adults, PWV and carotid IMT may provide partly similar information on vascular damage. In addition, we conclude that PWV and Cdist, as markers of segmental and local arterial stiffness, are, at least in part, representatives of a similar adverse vascular wall process. In order to arrive at a more accurate and comprehensive understanding of vascular health, future epidemiological studies should be conducted with a combination of complementary non-invasive methods to evaluate the structural and functional alterations in the vascular wall, particularly in young adults.

Conflicts of interest

None.

Acknowledgements

This study was financially supported by the Academy of Finland (grant nos. 77841, 117832, 201888, 121584, 124282 and 126925); the Social Insurance Institution of Finland; the Turku University Foundation; the Tampere University Medical Fund; the Kuopio, Tampere (EVO grants 9M048, 9L054 and 9J055) and Turku University Hospital Medical Funds; the Paavo Nurmi Foundation; the Emil Aaltonen Foundation; the Juha Vainio Foundation; the Finnish Foundation of Cardiovascular Research; the Finnish Cultural Foundation; and the Orion-Farmos Research Foundation (T. Koivistoinen).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.08.007.

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Supplementary data

Carotid artery studies

In the YFS cohort ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson, CA, USA) with 13.0 MHz linear array transducer (1, 2). To measure carotid IMT, the image was focused on the posterior (far) wall of left carotid artery. A magnified image was recorded from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. The digitally stored scans were manually analyzed by one reader blinded to participants' details. From the 5-second clip image, the best quality end-diastolic frame was selected (incident with the R wave on a continuously recorded electrocardiogram). From this image, at least 4 measurements of the common carotid far wall were taken approximately 10 mm proximal to the bifurcation to derive mean carotid IMT. The between-visit coefficient of variation (CV) of IMT measurements was 6.4 % (3). To assess carotid artery distensibility, the best-quality cardiac cycle was selected from the 5-second image clips (4). The common carotid diameter 10 mm from carotid bifurcation was measured from the B-mode images with ultrasonic calipers at least twice in end diastole and end systole, respectively. The means of the measurements were used as the end-diastolic and end-systolic diameters. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the carotid artery distensibility: Cdist (%/10 mmHg) = $[(D_s - D_d)/D_d]/(P_s - P_d)$, where D_s is the systolic diameter, D_d is the diastolic diameter, P_s is systolic blood pressure and P_d is diastolic blood pressure. In our laboratory, the between-visit CV was 16.3 % for Cdist measurements (4).

In the Health 2000 Survey cohort high-resolution B-mode carotid ultrasound examination of the right carotid artery was performed according to standardized

protocol using a 7.5 MHz linear array transducer (5, 6). To measure carotid IMT, the distal 10 mm of the common carotid artery using the beginning of the carotid bulb as an anatomical landmark was examined. The transducer was positioned to visualize both the far and near wall lumen-intima and media-adventitia interfaces at a single (lateral) angle. A cine loop was recorded for 4-5 s and stored on super VHS tape. The computer program PROWIN 23.1 was used to track the far wall lumen-intima and media-adventitia echoes to determine carotid IMT over the distal 10 mm segment of the common carotid artery. The mean carotid IMT was measured from three digitized end-diastole images (incident with the R wave on a continuously recorded electrocardiogram). The between-visit CV of IMT measurements was 9.2 % (5). To assess carotid artery distensibility, the computer program PROWIN 23.1 was used to determine the arterial diameter over the distal 10 mm length of the common carotid artery from the peak systole and end-diastole images (6). Systolic and diastolic arterial diameters were calculated as the mean of three average systolic and diastolic arterial diameters, respectively. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the carotid artery distensibility: Cdist (%/10 mmHg) = $[(D_s - D_d)/D_d]/(P_s - P_d)$. Selzer et al. (7) have previously reported between-visit CV of 11.05 % for Cdist measurement using the similar measurement protocol.

Measurement of brachial flow-mediated dilation

To assess brachial artery FMD, the left brachial artery diameter was measured both at rest and during reactive hyperemia (8). Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 minutes, followed by a release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at rest and 40, 60

and 80 seconds after cuff release. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to resting scan (100 percent). The greatest value between 40 to 80 seconds was used to derive the maximum FMD. In our laboratory, the between-visit CV was 3.2 % for brachial artery diameter measurements, and 26.0 % for FMD measurements (8). Brachial FMD was measured only in the YFS cohort.

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Metabolism Clinical and Experimental 56 (2007) 320–326
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Metabolic syndrome and arterial stiffness: The Health 2000 Survey

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Received 27 May 2006; accepted 25 October 2006

Abstract

Metabolic syndrome and its components have been associated with arterial stiffness and cardiovascular disease. The objective of this study was to examine the independent influences of metabolic syndrome, its components, and other cardiovascular risk factors on arterial stiffness as well as to compare 2 definitions for metabolic syndrome (National Cholesterol Education Program [NCEP] and International Diabetes Federation [IDF]) in their ability to identify subjects with arterial stiffness. The study population consisted of 401 Finnish men and women aged 45 years and older who participated in a substudy of the Finnish population–based Health 2000 Survey. Pulse wave velocity (PWV) measured by whole-body impedance cardiography was used as a marker of elevated arterial stiffness. In multivariate models, systolic blood pressure, age, waist circumference, and fasting blood glucose ($P \leq .001$ for all) were independent determinants for PWV. In the models including metabolic syndrome instead of its components, the NCEP and IDF definitions were similarly associated with PWV ($P \leq .01$ for both), the other independent determinants being age, sex ($P < .001$ for both) and plasma C-reactive protein concentration ($P = .016$ and $P = .005$ in models containing the NCEP and IDF definitions, respectively). Systolic blood pressure, age, waist circumference, and fasting blood glucose level were independently associated with increased arterial stiffness. Metabolic syndrome determined increased arterial stiffness independently of other known cardiovascular risk factors. The NCEP and IDF definitions did not differ in their ability to identify subjects with increased arterial stiffness.

1. Introduction

Metabolic syndrome is a cluster of cardiovascular risk factors such as central obesity, hypertension, dyslipidemias, and glucose intolerance. It has been shown to be a predictor of type 2 diabetes mellitus [1], coronary heart disease [2], and mortality [3-5]. Metabolic syndrome has various definitions. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III proposed their widely used clinical definition for metabolic syndrome in 2001 [6]. Recently, the International Diabetes Federation (IDF) also published a worldwide definition of metabolic syndrome [7]. These definitions have 2 basic differences. First, the IDF definition has a significantly lower cutoff point for waist circumference than the NCEP definition. Second, the IDF definition makes the presence of increased waist circumference mandatory for diagnosis, whereas the NCEP definition considers waist circumference as important as the other components.

Arterial stiffness has been a strong independent predictor of coronary events and cardiovascular mortality in several

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0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.10.008

patient groups [8-11]. It can be evaluated by measuring pulse wave velocity (PWV) along the arterial tree. The individual components of metabolic syndrome have been previously associated with increased arterial stiffness and higher PWV values [12,13]. Hypertension in particular has been linked to increased arterial stiffness [14]. Metabolic syndrome as a whole, mostly according to the NCEP criteria, has also been associated with arterial stiffness [13,15-18]. The NCEP and the IDF criteria have been compared in few studies so far. Both definitions have been similarly associated with coronary heart disease [19] and mortality [20]. To our knowledge, these criteria have not been compared regarding their ability to identify subjects with increased arterial stiffness.

The aim of this study was to evaluate the relationships among metabolic syndrome, its individual components, and arterial stiffness. Furthermore, we set out to discover whether the NCEP and the IDF definition can identify subjects with increased arterial stiffness similarly. We also intended to test the applicability of the whole-body impedance cardiography (ICG_{WB}) method for measuring PWV in a large epidemiological study.

2. Methods

2.1. Study population

We studied a subpopulation of a large Finnish cross-sectional health examination survey (the Health 2000 Survey) carried out in 2000-2001 [21]. The overall study cohort was a two-stage stratified cluster sample (8028 persons) representing the entire Finnish population aged 30 years and older. To study cardiovascular disease (CVD) and diabetes more thoroughly, a supplemental study was carried out (sample size, 1867; participation rate, 82%). The subjects, a subpopulation of the Health 2000 Survey, in the supplemental study were 45 years and older, and the study was executed in the catchment areas of the 5 Finnish university hospitals because specialized equipment was required. In the catchment areas of Tampere and Turku university hospitals, 401 individuals (176 men and 225 women; mean age, 58 years; range, 46-76 years) participated in the supplemental study and underwent the ICG_{WB} measurements. These individuals were selected to be our study group.

Waist circumference was not measured in the supplemental study; therefore, the Health 2000 Survey parameters were used to define the presence of metabolic syndrome. All the other measurements and laboratory tests used in the present study were collected from the data of the supplemental study. The mean time interval between the Health 2000 Survey and the supplemental study was 1 year and 4 months (range, 10-23 months). The mean ($\pm$SD) change in body weight during this time was 0.52 ($\pm$3.43) kg. Because this change was not clinically significant, it is likely that change in waist circumference was not clinically significant either. Because most of the women in our study population had reached menopause, we did not analyze premenopausal and postmenopausal women separately. To evaluate a possible conflicting influence of concomitant diseases on the associations between the risk factors and PWV, we also created a smaller sample excluding subjects with CVD and diabetes. Subjects with previous myocardial infarction or stroke, or with diagnosed diabetes, coronary heart disease, cardiac insufficiency, cardiac arrhythmia, hypertension, arterial stenosis, or thrombosis in a lower limb or other CVD were excluded. The subjects who had fasting plasma glucose concentration of 7 mmol/L or higher or who had 2-hour glucose value of 11.1 mmol/L or higher in the oral glucose tolerance test were excluded. From this smaller sample, we also excluded subjects who were on antihypertensive medication or statins. After these additional exclusions, 200 individuals free of CVD and diabetes remained with available PWV data.

2.2. Metabolic syndrome

We used 2 different criteria to define metabolic syndrome. According to the NCEP definition [6], a person has metabolic syndrome if at least 3 of the following criteria are met: waist circumference greater than 102 cm for men and greater than 88 cm for women; triglycerides, 1.7 mmol/L or greater; high-density lipoprotein (HDL) cholesterol, less than 1.03 mmol/L for men and less than 1.29 mmol/L for women; systolic blood pressure, 130 mm Hg or higher, and diastolic blood pressure, 85 mm Hg or higher; and fasting glucose, 5.6 mmol/L or higher. The fasting glucose threshold of the NCEP criterion was modified in 2004 [22].

According to the IDF definition [7], a person has metabolic syndrome if waist circumference is increased ($\geq$94 cm for men and $\geq$80 cm for women) and at least 2 of the following factors are present: triglycerides, 1.7 mmol/L or greater, or specific treatment of this lipid abnormality; HDL cholesterol, less than 1.03 mmol/L in men and less than 1.29 mmol/L in women, or specific treatment; systolic blood pressure 130 mm Hg or higher or diastolic blood pressure 85 mm Hg or higher, or treatment of previously diagnosed hypertension; fasting plasma glucose, 5.6 mmol/L or higher, or previously diagnosed type 2 diabetes mellitus. The IDF definition has ethnicity-specific cutoff points for waist circumference.

2.3. Pulse wave velocity

Pulse wave velocity was measured by ICG_{WB} using a commercially available circulation monitor device (CircMon B202, JR Medical, Tallinn, Estonia). Subjects were first interviewed and then electrodes (Blue Sensor type R-00-S; Medicotest, Ölstykke, Denmark) were applied while subjects were in the supine position for at least 15 minutes before the 10-minute PWV measurements. A pair of electrically connected current electrodes was placed on the distal part of the extremities just proximal to the wrists and ankles. Voltage-sensing electrodes were placed proximally to the current electrodes, with a distance of 5 cm

Table 1
Clinical and laboratory parameters of the study cohort (n = 400) with and without metabolic syndrome (MetS) according to 2 definitions (NCEP, IDF)

	MetS by NCEP definition			MetS by IDF definition		
	Yes (n = 156-162)[a]	No (n = 227-238)[a]	*P*	Yes (n = 175-182)[a]	No (n = 208-218)[a]	*P*
Age (y)	59.5 ± 7.7	57.6 ± 7.9	.017	59.5 ± 7.6	57.4 ± 8.0	.009
Sex (men, %)	44	44	.883	46	43	.555
Current smoking (%)	24	23	.748	24	23	.689
BMI (kg/m^2)	29.3 ± 3.9	25.6 ± 3.7	<.001	29.0 ± 3.8	25.5 ± 3.9	<.001
Waist circumference (cm)	101.5 ± 11.2	89.2 ± 10.8	<.001	100.9 ± 10.8	88.5 ± 11.0	<.001
Heart rate (beats/min)	64.9 ± 10.1	63.3 ± 10.7	.133	64.6 ± 9.7	63.4 ± 11.1	.260
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.7 ± 0.5	<.001	1.4 ± 0.4	1.7 ± 0.5	<.001
LDL cholesterol (mmol/L)	3.6 ± 0.9	3.3 ± 0.9	.008	3.5 ± 0.9	3.3 ± 0.9	.028
Total cholesterol (mmol/L)	5.7 ± 1.0	5.5 ± 0.9	.213	5.6 ± 1.0	5.6 ± 0.9	.429
Triglycerides (mmol/L)	1.7 ± 0.8	1.2 ± 0.5	<.001	1.7 ± 0.8	1.1 ± 0.5	<.001
Fasting glucose (mmol/L)	6.3 ± 1.7	5.5 ± 0.7	<.001	6.2 ± 1.6	5.5 ± 0.7	<.001
CRP (mg/L)	4.1 ± 5.6	2.2 ± 3.0	<.001	4.0 ± 5.4	2.1 ± 2.8	<.001
SBP (mm Hg)	142.3 ± 19.5	129.1 ± 18.4	<.001	140.2 ± 19.3	129.6 ± 19.1	<.001
DBP (mm Hg)	85.1 ± 9.2	81.0 ± 9.7	<.001	85.0 ± 8.7	80.1 ± 10.0	<.001
PP (mm Hg)	57.2 ± 15.4	48.2 ± 11.8	<.001	55.3 ± 15.4	48.9 ± 12.1	<.001

Values are means ± SD except values for sex and smoking, which are percentages. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

[a] Variation of n is caused by the fact that some values are missing for some subjects.

between the centers of the electrodes. With this electrode configuration, the recorded heart-synchronous changes in impedance reflect the weighted sum of the pulsatile plethysmograms of the vessels between the electrodes, ie, almost the whole vascular system. The foot of the whole-body impedance cardiogram coincides with pulse transmission in the aortic arch, making it possible to estimate the beginning of pulse wave transmission in the arterial system. Similarly, with voltage sensing electrodes applied to any distal region between the current electrodes, pulse-related impedance changes can be recorded. In this study, the distal impedance plethysmogram was recorded from a popliteal artery at knee joint level. The active electrode was placed on the lateral side of the knee joint and the reference electrode on the calf, the distance between the electrodes being about 20 cm. The time difference between the feet of these impedance plethysmograms, recorded from the aortic arch and popliteal artery, was measured. The time resolution of the CircMon recordings was 5 milliseconds. The evaluation of the ICG_{WB} method and PWV measurement using ICG_{WB} has been described in detail previously [23,24]. Reproducibility values of the PWV measurements by ICG_{WB} (2.42 m/s) and Doppler ultrasound (2.17 m/s) are similar [24].

2.4. Waist circumference, body mass index, blood pressure, and smoking

Waist circumference was measured with subjects in the standing position by using the standards created for population health studies [25]. Height and weight were measured and body mass index (BMI) was calculated. In the Health 2000 Survey, blood pressure was measured from the right arm with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany). The first measurement was taken after subjects had rested at least 5 minutes in the sitting position. Korotkoff's first phase was used as the sign of systolic blood pressure and the fifth phase as the sign of diastolic pressure. The measurement was repeated 2 minutes after the first measurement. The average of the 2 measurements was used in the analysis. In the supplemental study, blood pressure was measured from the right arm after at least 10 minutes' rest. The measurement was taken 3 times with 1- to 2-minute intervals. The automatic Omron M4 manometer (Omron Matsusaka, Japan, and Omron Healthcare Europe, Hoofddorp, the Netherlands) was used in these measurements. The average of the 3 measurements was used in the analysis. Pulse pressure was calculated as the difference between the average systolic and the average diastolic blood pressure. Current smoking was evaluated with a questionnaire. Those who were currently smoking were defined as smokers and the rest of the subjects as nonsmokers. The smoking data used in the present study were collected from the Health 2000 Survey data.

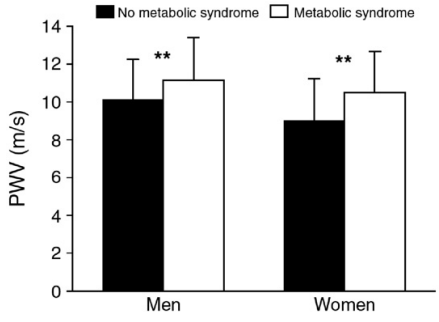

Fig. 1. PWV (mean and SD) in men and women with or without metabolic syndrome, according to the NCEP definition. **P < .01. The pattern is essentially the same using the IDF definition.

Table 2
Univariate correlations between cardiovascular risk factors and PWV in the whole cohort (n = 393-401) and in the healthy subsample (n = 197-200)

	Whole cohort		Subsample	
	r	*P*	*r*	*P*
Age (y)	0.510	<.001	0.518	<.001
BMI (kg/m^2)	0.238	<.001	0.274	<.001
Waist circumference (cm)	0.343	<.001	0.353	<.001
HDL cholesterol (mmol/L)	−0.161	.001	−0.255	<.001
LDL cholesterol (mmol/L)	0.062	.217	0.208	.003
Total cholesterol (mmol/L)	0.028	.577	0.120	.090
Triglycerides (mmol/L)	0.199	<.001	0.174	.014
Fasting glucose (mmol/L)	0.341	<.001	0.252	<.001
CRP (mg/L)	0.226	<.001	0.214	.003
SBP (mm Hg)	0.627	<.001	0.694	<.001
DBP (mm Hg)	0.392	<.001	0.496	<.001
PP (mm Hg)	0.619	<.001	0.642	<.001
HR × PP	0.627	<.001	0.664	<.001

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure.

2.5. Laboratory tests

Venous blood samples were drawn from the antecubital vein after an overnight fast. HDL cholesterol, total cholesterol, triglyceride, and glucose concentrations were determined enzymatically (Roche Diagnostics, Mannheim, Germany, for HDL; Olympus System Reagent, Hamburg, Germany, for total cholesterol, triglyceride, and glucose) with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). C-reactive protein (CRP) concentrations were determined by a chemiluminescent immunometric assay (Immulite, Diagnostic Products, Los Angeles, CA). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald formula.

2.6. Statistical analyses

Statistical analyses were performed using SPSS for Windows (version 13.0; SPSS, Chicago, IL). The skewed distributions of triglycerides and CRP were corrected logarithmically before statistical analyses. Chi-square and *t*-test analyses were calculated to compare categorical and continuous variables between the metabolic syndrome groups, respectively. Pearson correlation coefficients were used to examine the association between cardiovascular risk factors and PWV. Stepwise linear regression analysis was performed for continuous and dichotomous variables to examine independent relationships among metabolic syndrome, its components, other cardiovascular risk factors, and PWV.

3. Results

The prevalence of metabolic syndrome obtained by using the NCEP and IDF definitions was, respectively, 41% and 47% in men and 40% and 44% in women. For one participant, the waist circumference measurement was missing and the presence of metabolic syndrome could not be assessed. By both definitions, the subjects with metabolic syndrome were older, had higher BMI, waist circumference, LDL cholesterol, triglycerides, fasting plasma glucose, CRP and blood pressure and lower HDL cholesterol ($P < .05$ for all) than the subjects who did not have the syndrome. Subjects with and without metabolic syndrome did not differ in sex, resting heart rate, total cholesterol levels, or smoking habits ($P > .1$ for all). Twenty-eight percent of the study population was on antihypertensive medication, and 11% used statins. Selected clinical and demographic values of the study population are given in Table 1.

Men had significantly higher mean PWV than women ($P < .001$). For both sexes, the mean PWV was significantly higher in subjects with metabolic syndrome (using both definitions; $P < .01$) than those without the syndrome (Fig. 1 illustrates the data obtained with the NCEP definition). There was no statistically significant difference in the mean PWV ($P > .1$) of current smokers and nonsmokers. Age, systolic blood pressure, diastolic blood pressure, pulse pressure, product of heart rate and pulse pressure, waist circumference, BMI, and levels of HDL cholesterol, triglycerides, CRP, and fasting plasma glucose correlated statistically significantly with PWV (Table 2). Correlations between risk factors and PWV remained essentially similar in the smaller group excluding subjects with CVD and diabetes with the exception that the plasma LDL cholesterol level correlated statistically significantly with PWV (Table 2).

A stepwise linear regression model was performed to examine the relationships between cardiovascular risk

Table 3
A linear regression model for the relationships between cardiovascular risk factors and PWV in the whole cohort (n = 390) and in the healthy subsample (n = 196)

Risk variable	Whole cohort			Risk variable	Subsample		
	$\beta \pm$ SE	*P*	R^2 change (%)		$\beta \pm$ SE	*P*	R^2 change (%)
SBP (mm Hg)	.05 ± .00	<.001	40	SBP (mm Hg)	.06 ± .01	<.001	48
Age (y)	.10 ± .01	<.001	11	Age (y)	.10 ± .01	<.001	12
Fasting glucose (mmol/L)	.27 ± .07	<.001	3	Waist circumference (cm)	.02 ± .01	.042	1
Waist circumference (cm)	.03 ± .01	<.001	1				
R^2 (%)	55%				61		

Initial stepwise regression models included age, sex, waist circumference, fasting plasma glucose, HDL cholesterol, systolic blood pressure, CRP, triglycerides, smoking and LDL cholesterol (only in the sub sample) as independent variables. β indicates regression coefficient; R^2 change, change in adjusted R^2 value after addition of the respective variable in to the model; R^2, adjusted R^2 value of the whole model.

Table 4
Linear regression model for the relationships between metabolic syndrome (MetS), using 2 different definitions, other cardiovascular risk factors and PWV in the whole cohort (n = 392) and in the healthy sub sample (n = 197)

Risk variable	Whole cohort			Risk variable	Subsample		
	$\beta \pm$ SE	P	R^2 change (%)		$\beta \pm$ SE	P	R^2 change (%)
Age (y)	.14 ± .01	<.001	26	Age (y)	.13 ± .02	<.001	26
MetS using the NCEP definition	.92 ± .20	<.001	4	MetS using the NCEP definition	.84 ± .25	<.001	5
Sex	−.82 ± .19	<.001	3	Sex	−.72 ± .23	.002	2
CRP (mg/L)	.52 ± .21	.016	0.8				
R^2 (%)	34				33		
Age (y)	.14 ± .01	<.001	26	Age (y)	.13 ± .02	<.001	26
Sex	−.80 ± .19	<.001	3	MetS using the IDF definition	.78 ± .24	.001	4
MetS using the IDF definition	.67 ± .20	.001	3	Sex	−.69 ± .24	.004	3
CRP (mg/L)	.60 ± .21	.005	1				
R^2 (%)	33				33		

Initial stepwise regression models included age, sex, CRP, smoking, metabolic syndrome, according to the NCEP or the IDF definition and LDL cholesterol (only in the subsample) as independent variables. β indicates regression coefficient; R^2 change, change in adjusted R^2 value after addition of the respective variable in to the model; R^2, adjusted R^2 value of the whole model.

factors as independent variables and PWV (Table 3). The initial stepwise regression model included age, sex, waist circumference, fasting plasma glucose, HDL cholesterol, triglycerides, systolic blood pressure, CRP, and smoking as independent variables. In that model, systolic blood pressure, age, fasting blood glucose, and waist circumference explained 55% (adjusted R^2, 55%) of the variation in PWV. When the same model was adjusted by replacing systolic blood pressure with pulse pressure or with the product of heart rate and pulse pressure (data not shown), the results remained essentially the same (adjusted R^2, 53% and 55%, respectively) with the exception that sex was also an independent determinant of PWV. We used the same linear regression model (LDL cholesterol included) for the smaller sample excluding subjects with CVD and diabetes (Table 3). Systolic blood pressure, age, and waist circumference explained 61% of the variation in PWV. Therefore, in this smaller healthier population, fasting plasma glucose was not an independent factor determining PWV.

Another stepwise linear regression model was performed by using metabolic syndrome (both definitions separately) and other known cardiovascular risk factors (age, sex, CRP, and smoking) as independent variables (Table 4). Age, metabolic syndrome (using the NCEP or the IDF definition), sex, and CRP were independent determinants for PWV (adjusted R^2, 34% and 33% in the models containing the NCEP and the IDF definition, respectively). When CRP was excluded from the models, the results remained essentially the same. The same linear regression model (including LDL as independent variable) was used for the smaller sample that excluded subjects with CVD and diabetes (Table 4). Age, metabolic syndrome, and sex explained 33% (using the NCEP or the IDF definition) of the variation in PWV.

4. Discussion

Metabolic syndrome and its individual components are risk factors for atherosclerosis and CVD [1-5]. Arterial stiffness is also related to CVD and atherosclerosis [26] and has been a strong independent predictor of coronary events and cardiovascular mortality in several patient groups [8-11]. In this study, we examined the relationships between arterial stiffness measured by PWV and single cardiovascular risk factors as well as metabolic syndrome as a whole. Our aim was also to compare 2 different definitions for metabolic syndrome (NCEP and IDF) in their relations with arterial stiffness.

Age, systolic blood pressure, diastolic blood pressure, pulse pressure, product of heart rate and pulse pressure, BMI, waist circumference, and triglyceride, HDL cholesterol, fasting plasma glucose, and CRP levels correlated statistically significantly with PWV. The univariate associations were thus significant between PWV and all the components of metabolic syndrome. The strongest correlation was observed between systolic blood pressure and PWV, which is not surprising considering that both are connected to arterial stiffness. As expected, age was strongly correlated with PWV. In all, these findings are well in line with previously published data [14,27]. LDL cholesterol has also been linked with arterial stiffness [28,29]. In a smaller sample excluding subjects with CVD and diabetes, we also found a significant correlation between LDL cholesterol and PWV.

The mean PWV was significantly higher in the subjects with metabolic syndrome than in those without the syndrome, regardless of the definition used. This is in line with previous studies using the NCEP definition [13,14,16-18]. To our knowledge, this is the first study to examine the relationships between metabolic syndrome and arterial stiffness by using the IDF definition. In our study, men had significantly higher mean PWV than women. The results of the Framingham heart study were in agreement with the present study, the difference in PWV being small but statistically significant [30]. On the other hand, several other studies have not reported significant differences between the sexes [31,32].

Although we did find that many individual risk factors were associated with arterial stiffness, only some of them

appeared in the final regression models as independent determinants of PWV. As expected, systolic blood pressure and age were the strongest factors determining arterial stiffness—a finding that is in agreement with previous data [33]. In our study population, waist circumference and fasting plasma glucose were also independent determinants of arterial stiffness, results consistent with those of previous studies [13-15,34]. When metabolic syndrome was included in the regression model instead of its components, it was found to be an independent determinant of arterial stiffness (using both definitions) together with age, sex, and CRP concentration. In the smaller sample that excluded CVD and diabetes, fasting plasma glucose was not an independent factor determining PWV. This can be partly explained by the smaller sample size. On the other hand, metabolic syndrome remained as an independent factor even in this population free of CVD and diabetes. Similar results have been reported previously [18].

We did not find a significant difference between the NCEP and the IDF definitions in their ability to determine arterial stiffness. To our knowledge, this has not been studied previously. The main difference between these 2 definitions is that the latter makes central obesity mandatory for diagnosis. The IDF definition also has a lower waist circumference threshold. Because of this, the IDF definition produces a higher prevalence for metabolic syndrome than the NCEP definition. In our study population, the prevalence figures were 45.4% and 40.4%, respectively, which are relatively high when compared with most of the earlier studies. This is probably related to the age structure of our study population (older than 45 years). Nevertheless, this increases our understanding of the magnitude of metabolic syndrome as an important CVD risk factor.

C-reactive protein correlated significantly with PWV in the present study. The association of CRP and arterial stiffness has been reported previously [35-37]. Some [36,37] of the previous studies have suggested that CRP is associated with arterial stiffness independently of other CVD risk factors. In our population, however, CRP was not independently associated with arterial stiffness when all the other risk factors were taken into account. In the regression models with metabolic syndrome included instead of its components, CRP was an independent determinant. This is probably due to significant associations between CRP and all the components of metabolic syndrome.

Previously, PWV measurements have been done mostly by methods using Doppler ultrasound or mechanoelectrical pulse transducers [38,39]. PWV can also be measured by ICG_{WB}, which provides a handy and reliable tool for evaluating arterial stiffness on the basis of PWV simultaneously with cardiac output and related hemodynamic parameters. The ICG_{WB} method turned out to be applicable especially for large epidemiologic studies because it is not user dependent and does not require large personnel resources. The method is highly repeatable and reproducible [24].

In conclusion, our findings indicate that blood pressure, age, waist circumference, and fasting plasma glucose concentration are important independent factors for determining arterial stiffness in a middle-aged and elderly population. The NCEP and IDF definitions were both similarly associated with PWV, independently of other known cardiovascular risk factors. This suggests that both the NCEP and IDF definitions are able to identify subjects with increased arterial stiffness in a Finnish population. However, although metabolic syndrome is an important factor affecting cardiovascular health and its prevalence remarkably high in developed countries, its components have to be carefully evaluated as independent risk factors.

Acknowledgments

This study was financially supported by the Medical Research Fund of the Tampere University Hospital.

We thank the personnel on the field and the support organizations of the Health 2000 Survey in the National Public Health Institute of Finland.

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Clin Physiol Funct Imaging (2011) **31,** pp464–471 doi: 10.1111/j.1475-097X.2011.01042.x

Arterial tension time reflects subclinical atherosclerosis, arterial stiffness and stroke volume

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Accepted for publication
Received 7 February 2011; accepted 23 June 2011

Key words
cardiovascular health; carotid artery; haemodynamics; risk factors; whole-body impedance cardiography

Summary

Objective: To introduce and evaluate a new haemodynamic parameter known as arterial tension time (ATT) and study whether ATT is associated with traditional cardiovascular risk factors as well as with indices of arterial stiffness, cardiac pump function and subclinical atherosclerosis.

Methods: Arterial tension time was measured from the whole-body impedance cardiography (ICG) signal and defined as the time difference between the onset of arterial distension induced by stroke volume (SV) and maximal integrated arterial distension. As measures of subclinical atherosclerosis and arterial stiffness, carotid artery intima-media thickness (IMT), Young's elastic modulus (YEM), arterial stiffness index (ASI) and carotid artery compliance (CAC) were assessed with ultrasound in 336 Finnish adults (aged 46–76 years, 43·2% men) participating in the Health 2000 Survey. In addition, pulse wave velocity (PWV) and stroke volume index (SI), as indices of arterial stiffness and cardiac pump function, were assessed with ICG.

Results: Arterial tension time was associated inversely with PWV, IMT, YEM and ASI ($P<0{\cdot}002$ for all) and directly with SI and CAC ($P<0{\cdot}001$ for both). Age, systolic blood pressure, diastolic blood pressure and fasting glucose were independent determinants of decreased ATT ($P<0{\cdot}04$ for all). Moreover, accumulation of cardiovascular risk factors was associated with the decrease in ATT (P for trend $<0{\cdot}001$).

Conclusion: Decreased ATT was associated with increased arterial stiffness, increased subclinical atherosclerosis and decreased SV. Current results suggest that ATT provides simultaneous information on several aspects of cardiovascular structure and function and could possibly serve as a new integrated parameter for cardiovascular risk stratification.

Introduction

The arterial pulse pressure (PP) wave is a result of the interaction between left ventricular (LV) stroke volume (SV) and the stiffness and atherosclerotic plagues of the arterial tree. Ageing and accumulation of cardiovascular risk factors are associated with adverse structural and functional alterations in the vascular wall, which predispose to arterial stiffening and atherosclerosis (Davis *et al.*, 2001; Zieman *et al.*, 2005; O'Rourke & Hashimoto, 2007). As a consequence of increased arterial stiffness and plaques in the branches of large arteries, pulse wave reflections from the discontinuities of the arterial tree occur earlier, thereby increasing systolic blood pressure (SBP) (Dart & Kingwell, 2001). In contrast, greater peripheral run-off of the SV during systole and the impaired buffering capacity of arteries result in a decrease in diastolic blood pressure (DBP) (McVeigh *et al.*, 2002). These abnormalities are, in turn, reflected as an increased LV load, LV hypertrophy, decreased contractility and impaired coronary flow, leading to the development of LV failure (Katz, 1990; Levy *et al.*, 1996; O'Rourke & Hashimoto, 2007).

To date, several different non-invasive methods and parameters – such as pulse wave velocity (PWV), carotid artery compliance (CAC), Young's elastic modulus (YEM), arterial stiffness index (ASI), carotid artery intima-media thickness

(IMT) and SV – have been applied for the estimation of arterial stiffness, arterial wall structure and cardiac pump function. Previously, increased PWV, as a measure of increased segmental arterial stiffness, has proven a strong predictor of cardiovascular events and all-cause mortality (Vlachopoulos *et al.*, 2010), but studies on the associations between indices of local (carotid artery) stiffness, cardiovascular disease and mortality have reported conflicting results (Blacher *et al.*, 1998; Störk *et al.*, 2004; Dijk *et al.*, 2005; Mattace-Raso *et al.*, 2006; Ogawa *et al.*, 2009). In addition, although IMT is a widely used measure of subclinical atherosclerosis in clinical practice and has been shown to be an independent predictor of cardiovascular events (Lorenz *et al.*, 2007), there is accumulating evidence that IMT may not be useful for the risk stratification of individuals in the general population (Helfand *et al.*, 2009; Lorenz *et al.*, 2010; Simon *et al.*, 2010). One of the major concerns is the relatively modest predictive value of absolute risk (Lorenz *et al.*, 2010; Simon *et al.*, 2010). Moreover, although decreased SV, as an indicator of impaired cardiac pump function, has been demonstrated to be related to several cardiovascular risk factors (Heckbert *et al.*, 2006), associations between SV and cardiovascular events have been studied to a lesser extent. Therefore, ability of these indices of cardiovascular structure and function to predict cardiovascular risk is, to a degree, limited. It could hence be of clinical interest to develop an integrated cardiovascular parameter reflecting several aspects of the cardiovascular system – i.e. arterial stiffness, arterial wall structure and cardiac pump function – and thus possibly improve risk stratification.

In this study, our aim was to introduce and evaluate a new haemodynamic parameter based on whole-body impedance cardiography (ICG), namely arterial tension time (ATT), which is defined as the time difference between the onset of SV-induced arterial distension and maximal integrated arterial distension. We hypothesized that ATT provides simultaneous information on arterial stiffness, subclinical atherosclerosis and cardiac pump function. To address this, we studied whether ATT is related to traditional cardiovascular risk factors, as well as to ultrasound (IMT, CAC, YEM, ASI)- and ICG-derived (PWV, SV) indices of cardiovascular structure and function in a population of 336 Finnish adults.

Methods

Study population

The Health 2000 Survey was carried out in 2000–2001, and the overall study cohort was a two-stage stratified cluster sample (8028 subjects) representing the entire Finnish population aged 30 years and older (Aromaa & Koskinen, 2004). To study cardiovascular disease and diabetes more thoroughly, a supplemental study (1867 subjects, participation rate 82%) was carried out in the catchment areas of five Finnish university hospitals. The mean interval between the Health 2000 Survey and the supplemental study was 16 months (range 10–23 months). In the supplemental study, 350 subjects (aged 46–76 years) participated in carotid ultrasound and ICG examinations in the catchment areas of Tampere and Turku University Hospitals. After excluding subjects with incomplete cardiovascular risk factor data, a total of 336 subjects were included in the present analysis. Informed written consent was obtained from all subjects, and the study was approved by local ethics committees.

Clinical characteristics and laboratory tests

Blood pressure was measured after at least ten minutes of rest from the right arm using an automatic Omron M4 manometer (Omron Matsuka Co., Japan, Omron Healthcare Europe B.V., Hoofddorp, the Netherlands), and the mean of three measurements was used in the analysis. Height and weight were measured, and body mass index (BMI, kg m^{-2}) was calculated. Smoking was evaluated with a questionnaire and defined as smoking on daily basis. Smoking data in the present analysis were collected from the Health 2000 Survey data. Twenty-five subjects had self-reported cerebrovascular disease, coronary heart disease or a history of myocardial infarction. Twenty-eight subjects had diabetes mellitus: type 1 diabetes mellitus (n = 2), previously diagnosed type 2 diabetes mellitus (n = 9) or newly diagnosed type 2 diabetes mellitus on the basis of the oral glucose tolerance test carried out in the supplemental study (n = 17). Details of the oral glucose tolerance test and criteria for diabetes mellitus have been published previously (Koivistoinen *et al.*, 2011).

Venous blood samples were drawn after a 12-h fast. High-density lipoprotein (HDL) cholesterol and triglyceride concentrations were determined enzymatically (for triglycerides; Olympus System Reagent, Hamburg, Germany and for HDL cholesterol; Roche Diagnostics, Mannheim, Germany) with a clinical chemistry analyser (AU400; Olympus, Hamburg, Germany). Plasma glucose was determined by means of the glucose dehydrokinase method (Diagnostica Merck, Germany) in a clinical chemistry analyser (Konelab, Vantaa, Finland). Plasma insulin was determined with the radio immunoanalysis method (Pharmacia, Uppsala, Sweden) and C-reactive protein (CRP) concentrations with a chemiluminescent immunometric assay (Immulite, Diagnostic Products, Los Angeles, CA, USA). LDL cholesterol was calculated with the Friedewald formula.

Carotid artery studies

A high-resolution B-mode carotid ultrasound examination of the right carotid artery was performed according to a standardized protocol using a 7·5-MHz linear array transducer. The examinations were performed by centrally trained and certified sonographers, and one reader was responsible for reading all ultrasound images. IMT measurements were taken off-line with the aid of automated image processing software, and three summary measures of the IMT were calculated: (i) mean of the three average IMTs of the common carotid artery (mean CCA IMT), (ii) mean of the three average IMTs of the carotid bulb and (iii) mean of these two means. Mean CCA IMT was used in

the present study. Details of the method and the intrareader reproducibility values have been published previously (Niiranen *et al.*, 2007).

To assess carotid artery elasticity indices, the computer program PROWIN 23.1 (Prosound, CA, USA) was employed to determine the arterial diameter over the distal 1 cm length of the common carotid artery from peak systole and end-diastole images. The beginning of the carotid artery bulb (the site where the two parallel walls of the common carotid artery diverge) was used as an anatomical landmark. Systolic and diastolic arterial diameters (DAD) were calculated as the mean of three average systolic and DAD, respectively. On the basis of the ultrasound measurements and supine blood pressure measurements taken immediately before the ultrasound examination, the following indices of arterial elasticity were calculated: YEM (mmHg) = [Ep × DAD/(2 × IMT)], ASI = ln (SBP/DBP)/(ADC/DAD) and CAC (%/10 mmHg) = 10 × [(ADC/DAD)/PP], where Ep is Peterson's elastic modulus (PP × DAD)/ADC, ln is natural logarithm, DAD is diastolic arterial diameter and ADC is arterial diameter change (systolic arterial diameter − diastolic arterial diameter).

Young's elastic modulus gives an estimate of arterial stiffness that is independent of wall (intima-media) thickness (Salomaa *et al.*, 1995). ASI (also referred to as the β stiffness index) has been developed to reduce the impact of the curvilinear pressure–stiffness relationship on arterial stiffness, and it is therefore considered to be relatively independent of blood pressure (Hirai *et al.*, 1989; Salomaa *et al.*, 1995; Juonala *et al.*, 2005). CAC measures the ability of an artery to expand as a response to pulse pressure caused by cardiac contraction and relaxation (Juonala *et al.*, 2005).

Whole-body impedance cardiography measurements

Stroke volume, ATT and PWV were measured using the ICG method, and the examination was carried out with a commercially available circulation monitor device, the CircMon B202 (CircMon™; JR Medical Ltd, Tallinn, Estonia). Subjects were interviewed, after which they lay in a supine position for at least 15 min prior to the measurements. A pair of electrically connected current electrodes (Blue Sensor type R-00-S; Medicotest A/S, Ølstykke, Denmark) were placed on the distal parts of the extremities just proximal to the wrists and the ankles. Voltage electrodes were placed proximal to the current electrodes, with a distance of 5 cm between the centres of the electrodes (Fig. 1a). Alternating electrical current (30 kHz, 0·7 mA) was applied to the current electrodes, and the change in whole-body impedance was measured from the voltage electrodes. When SV enters the aortic arch and the aorta's diameter increases, the whole-body impedance decreases, which can be measured with voltage-sensing electrodes on the distal parts of the extremities. The CircMon software calculates SV using the following equation:

$$SV = k \times H^2 \times \frac{dZ/Z_c}{Z_0} \times \frac{C}{D}$$

where coefficient k is an empirical correction factor (k = 0·275 for men and k = 0·247 for women) (Tishchenko, 1973), H is subjects' height (cm), dZ is the amplitude of heart synchronous impedance variation (Ω) (Fig 1b), Z_c is the calibration factor (0·1 Ω), Z_0 is the baseline impedance of the body (Ω), C is the duration of the cardiac cycle (ms) (Fig 1b) and D is the duration from the lowest value of whole-body impedance to the onset of the next cardiac cycle (ms) (Fig. 1b). The ICG signal is inverted for better visual comparability with blood pressure and other pulsatile signals.

Arterial tension time was defined as the time difference between the onset of the decrease in whole-body impedance and the lowest value of whole-body impedance (C − D) that coincides with the time difference between the onset of

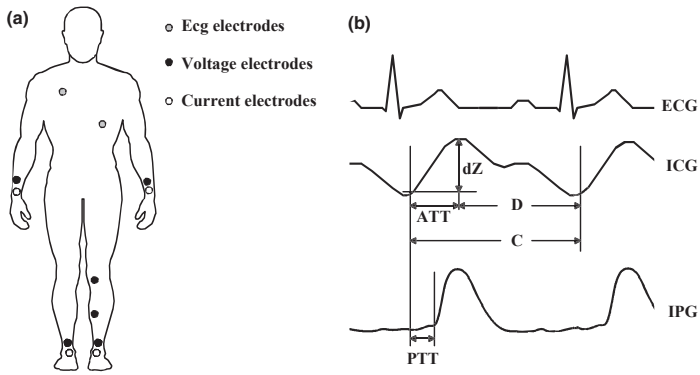

Figure 1 (a) Placement of the electrodes in whole-body impedance cardiography with an additional voltage-sensing channel on the left calf for pulse wave velocity measurement. (b) Synchronous recording of the electrocardiogram (ECG), whole-body impedance cardiogram (ICG) and impedance plethysmogram (IPG). The time difference between the feet of the ICG and IPG indicates the pulse transit time (PTT) from the aortic arch to the popliteal artery. dZ is the amplitude of heart synchronous impedance variation, C is the duration of the cardiac cycle, and D is the duration from the peak dZ to the onset of the next cardiac cycle. Arterial tension time (ATT) indicates the time difference between C and D.

SV-induced arterial distension and maximal integrated arterial distension (Fig. 1b). To reduce the influence of respiration and possible variation of heart rate, ATT was averaged over a period of 30 s. In the supplemental study of the Health 2000 Survey, the whole-body ICG measurements were taken twice in the supine position, at a mean interval of 15 min (n = 336). The repeatability of the ATT between the two measurements was assessed (n = 336). The mean difference of the two measurements was 0·6 ms (standard deviation 16·4 ms), the coefficient of variation 14·4% and the coefficient of repeatability 32·8 ms (Bland & Altman, 1986). Mean values between the two measurements were not statistically different (196·2 versus 196·8 ms, paired samples t-test P = 0·481).

An additional pair of electrodes was placed on the knee joint level and the calf to measure PWV (Fig. 1a). The CircMon software measures the time difference between the onset of the decrease in impedance in the whole-body impedance signal caused by the pulse wave in the aortic arch and, subsequently, the popliteal artery signal (Fig. 1b). By means of this time difference and the distance between the two measurement sites, the software calculates the PWV. The CircMon software also automatically calculates systemic vascular resistance (SVR) by dividing mean blood pressure by cardiac output. SV and SVR were indexed to the body surface area to reduce the influence of body size on measurement results. They were defined as follows: stroke volume index (SI) = SV/body surface area (ml m^{-2}); systemic vascular resistance index (SVRI) = 79·96*SVR*body surface area [(dyn*s cm^{-5})*m^2], where 79·96 is a conversion factor from mmHg l^{-1}/min^{-1} to dyn*s cm^{-5}. More detailed descriptions of the ICG method and the validation studies have been published previously (Kööbi *et al.*, 1997a,b, 1999; Kaukinen *et al.*, 2003; Kööbi *et al.*, 2003).

Statistics

All statistical analyses were performed with SPSS for Windows (version 16·0; SPSS Inc., Chicago, IL, USA). Skewed distributions of triglycerides, insulin and CRP were corrected logarithmically before statistical analyses. Bivariate relations between clinical variables and ATT were examined by means of linear regression analysis. A stepwise linear regression model, including cardiovascular risk factors that had a statistically significant (P<0·05) or borderline significant (P = 0·05) association with ATT in univariate regression models, was constructed to study the independent effects of risk factors on ATT. Age- and sex-adjusted mean ATT values were analysed using general linear models. In the general linear model, risk factors were defined as

Table 1 Characteristics of the study cohort and the univariate relations between clinical variables and arterial tension time (ATT) (n = 336).

		Correlation with ATT	
Variable	**Mean[a]**	**β ± SE**	***P*-value**
Age (years)	58·1 ± 7·8	−1·045 ± 0·203	<0·001
Male sex (%)	43·2	−5·195 ± 3·326	0·119
Body mass index (kg m^{-2})	26·9 ± 4·1	−1·326 ± 0·402	0·001
HDL cholesterol (mmol l^{-1})	1·6 ± 0·4	10·344 ± 3·690	0·005
LDL cholesterol (mmol l^{-1})	3·4 ± 0·9	−3·724 ± 1·890	0·050
Triglycerides (mmol l^{-1})[b]	1·2 (0·9–1·6)	−32·648 ± 8·683	<0·001
Fasting insulin (mmol l^{-1})[b]	7·5 (5·3–10·1)	−40·884 ± 7·365	<0·001
Fasting glucose (mmol l^{-1})	5·7 ± 1·2	−6·630 ± 1·331	<0·001
C-reactive protein (mg l^{-1})[b]	1·6 (0·8–3·3)	−6·399 ± 3·510	0·069
Systolic blood pressure (mmHg)	133·9 ± 19·7	−0·677 ± 0·075	<0·001
Diastolic blood pressure (mmHg)	82·3 ± 9·6	−1·156 ± 0·160	<0·001
Smoking (%)	22·3	6·041 ± 3·956	0·128
Diabetes (%)	8·3	−23·127 ± 5·846	<0·001
Antihypertensive medication (%)	28·0	−19·747 ± 3·521	<0·001
Statin medication (%)	9·5	−2·951 ± 5·630	0·601
Cardiovascular disease (%)	7·4	−13·761 ± 6·254	0·028
Heart rate (beats min^{-1})	63·8 ± 10·5	−1·128 ± 0·145	<0·001
SI (ml m^{-2})	41·4 ± 7·0	2·122 ± 0·207	<0·001
IMT (mm)	0·82 ± 0·17	−33·185 ± 9·349	<0·001
PWV (m s^{-1})	10·0 ± 2·2	−8·419 ± 0·575	<0·001
YEM (mmHg)	7040 ± 4590	−0·002 ± <0·001	<0·001
ASI	3·7 ± 0·5	−10·828 ± 3·282	0·001
CAC (%/10 mmHg)	0·9 ± 0·5	14·099 ± 2·992	<0·001

β, regression coefficient; SE, standard error; Cardiovascular disease, self-reported cerebrovascular disease, coronary heart disease or history of myocardial infarction; SI, stroke volume index; IMT, carotid intima-media thickness; PWV, pulse wave velocity; YEM, Young's elastic modulus; ASI, arterial stiffness index; CAC, carotid artery compliance.

[a]Values are presented as unadjusted mean ± SD or geometric mean (25th–75th percentile) or percentages of subjects.

[b]Log-transformed in the linear regression analysis.

values at or above the sex-specific 80th percentile for body mass index, SBP, DBP, LDL cholesterol, triglycerides, fasting insulin or fasting glucose. For low HDL cholesterol, the sex-specific 20th percentile cut-off point was used. Subjects with SI, IMT, PWV, YEM, ASI and CAC values in the extreme quartiles were classified into groups of best and worst quartiles of SI, IMT, PWV, YEM, ASI and CAC.

Results

The clinical characteristics of the study cohort and the univariate relations between clinical variables and ATT are presented in Table 1. ATT was inversely associated with age, BMI, triglycerides, insulin, glucose, SBP and DBP and directly with HDL cholesterol ($P<0{\cdot}01$ for all). Prevalence of diabetes and cardiovascular disease, as well as the frequency of antihypertensive medication, was inversely associated with ATT ($P<0{\cdot}03$ for all). Furthermore, ATT was inversely related to heart rate, IMT, PWV, YEM and ASI and directly to SI and CAC ($P<0{\cdot}002$ for all).

In the stepwise linear regression analysis, age ($P<0{\cdot}001$), SBP ($P = 0{\cdot}012$), DBP ($P = 0{\cdot}036$) and fasting glucose ($P = 0{\cdot}001$) were independent determinants of decreased ATT (Table 2). In addition, accumulation of cardiovascular risk factors was associated with decreased ATT (P for trend $<0{\cdot}001$) (Fig. 2a). As shown in Fig. 2b, subjects with low SI or CAC and high PWV, YEM or ASI, as well as large IMT (age- and sex-adjusted) had decreased ATT when compared with subjects with high SI or CAC and low PWV, YEM or ASI, as well as small IMT ($P<0{\cdot}04$ for all).

There was an inverse univariate association between ATT and SVRI [$(\beta \pm SE)$; $-0{\cdot}017 \pm 0{\cdot}002$, $P<0{\cdot}001$]. Moreover, subjects with high SVRI (SVRI $\geq$ 75th percentile) had decreased ATT when compared to those with low SVRI (SVRI $\leq$ 25th percentile) (182·6 versus 213·6 ms, respectively, $P<0{\cdot}001$). Association between body surface area and ATT was not statistically significant [$(\beta \pm SE)$; $-6{\cdot}555 \pm 7{\cdot}806$, $P = 0{\cdot}402$]. The general linear model analyses were repeated with heart rate adjustment for ATT (in addition to age and sex adjustment), producing essentially similar results, with the exception that the differences in ATT between the best and worst quartiles of YEM and ASI were diluted (YEM; 198·6 versus 191·5 ms, $P = 0{\cdot}099$. ASI; 197·5 versus 192·4 ms, $P = 0{\cdot}237$).

Table 2 Multivariable relations between cardiovascular risk factors and arterial tension time (ATT) (n = 336).

	ATT	
	β ± SE	***P*-value**
Multivariable relations		
Age (years)	−0·758 ± 0·207	<0·001
Systolic blood pressure (mmHg)	−0·331 ± 0·130	0·012
DBP (mmHg)	−0·537 ± 0·255	0·036
Fasting glucose (mmol l^{-1})	−3·970 ± 1·236	0·001

The final model for stepwise linear regression analysis initially included age, body mass index, systolic and diastolic blood pressure (DBP), HDL cholesterol, LDL cholesterol, triglycerides, fasting insulin and fasting glucose. β, unstandardized regression coefficient; SE, standard error.

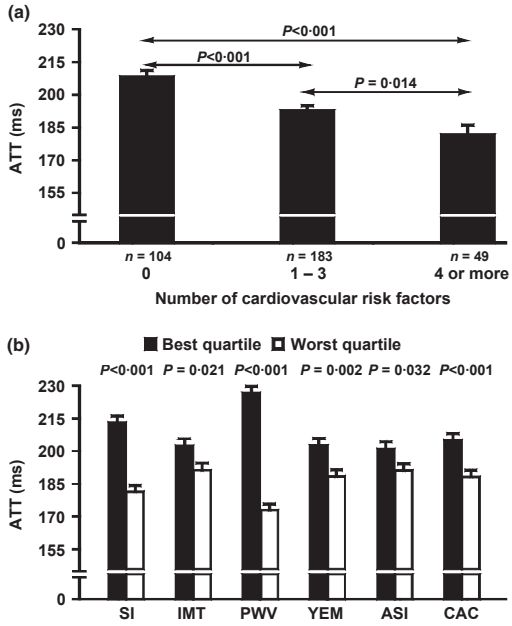

Figure 2 (a) Arterial tension time by the number of cardiovascular risk factors. (b) ATT according to the worst and best quartiles of SI, IMT, PWV, YEM, ASI and CAC. Values are expressed as age- and sex-adjusted means and standard errors. Risk factors were defined as values at or above the sex-specific 80th percentile for body mass index, systolic or diastolic blood pressure, LDL cholesterol, triglycerides, fasting insulin or fasting glucose. For low HDL cholesterol, the sex-specific 20th percentile cut-off point was used. ATT, arterial tension time; SI, stroke volume index; IMT, carotid intima-media thickness; PWV, pulse wave velocity; YEM, Young's elastic modulus; ASI, arterial stiffness index; CAC, carotid artery compliance.

Discussion

The main findings of this study on the relationships between traditional cardiovascular risk factors, arterial stiffness, subclinical atherosclerosis, cardiac pump function and ATT were as follows. Firstly, decreased ATT was associated with increased arterial stiffness as measured with two different independent methods. Secondly, decreased ATT was related to lower SI and increased IMT. Thirdly, accumulation of cardiovascular risk factors was associated with decreased ATT. The fourth main finding was that ageing, increased SBP, DBP and fasting glucose were independent determinants of decreased ATT.

The ICG measures blood flow and volume-induced changes in the arterial tree, producing a weighted sum of almost the whole arterial system. The foot of the ICG signal reflects the onset of SV-introduced arterial distension in the aortic arch, whereas the

peak of the ICG signal reflects the integrated maximum distension of arteries over the cardiac cycle. ATT was defined as the time difference between these two points in the ICG signal. In the case of a low SI, it is likely that the distending pressure of arteries is reduced, thus reducing the overall distending time of the arteries from minimum to maximum cross-sectional diameter. On the other hand, in the case of increased arterial load (reduced compliance/increased stiffness, increased SVRI or both), the capacity of the arteries to buffer pressure changes induced by cardiac contraction is reduced, possibly leading to a shorter distending time of the arterial wall as well. In support of these hypotheses, the findings of the present study suggest that decreased SI, as well as increased arterial stiffness and SVRI, is related to a decreased distending time of the arteries from minimum to maximum diameter.

In addition to arterial stiffness, carotid artery IMT is a widely accepted marker of subclinical atherosclerosis, reflecting not only local changes in the arterial wall but also the extent of atherosclerosis elsewhere in the arterial system (Craven *et al.*, 1990; Allan *et al.*, 1997). It has been previously shown that ageing and atherosclerosis are associated with several adverse alterations in the arterial wall, including the fragmentation of elastic lamellae, fibrous remodelling and the accumulation of plaques (O'Rourke, 1995). As these adverse changes in the arterial wall are also associated with arterial stiffening (O'Rourke, 1995; Zureik *et al.*, 2003; Zieman *et al.*, 2005), we may assume that increased atherosclerosis results in a reduced distending time of the arteries from the lowest to the highest diameter over the cardiac cycle. The relationship between IMT and ATT in the present study supports this assumption.

Previously, ageing, increased blood pressure, triglycerides, glucose and insulin have been shown to be associated with increased arterial stiffness (Li *et al.*, 2004; Juonala *et al.*, 2005; Aatola *et al.*, 2010; Koivistoinen *et al.*, 2011). In addition, age, triglycerides, BMI and SBP have been established as determinants of IMT (Davis *et al.*, 2001; Raitakari *et al.*, 2003; Sipilä *et al.*, 2009). Moreover, ageing, increased DBP and impaired fasting glucose have been demonstrated to be predictors of decreased SV (Lund-Johansen, 1988; Heckbert *et al.*, 2006). In line with these findings, we observed a significant inverse association in the current study between age, BMI, SBP, DBP, triglycerides, fasting insulin, fasting glucose and ATT. In addition, there was a direct association between HDL cholesterol and ATT. Further, prevalence of diabetes and cardiovascular disease, as well as the frequency of antihypertensive medication, was inversely associated with ATT. In the multivariable regression analysis, age, SBP, DBP and fasting glucose were found to be independent determinants of decreased ATT. Moreover, there was a decreasing trend for ATT with the accumulation of cardiovascular risk factors. On the whole, similar cardiovascular risk factor profiles, associated with the indices of arterial stiffness, IMT and SV, were found to be related to ATT. Nevertheless, future studies are required to investigate the pathophysiological mechanisms behind decreased ATT.

As a measure of segmental arterial stiffness, carotid–femoral PWV has proven a strong predictor of future cardiovascular events and all-cause mortality (Vlachopoulos *et al.*, 2010). However, findings with respect to local (carotid artery) stiffness have been inconsistent (Blacher *et al.*, 1998; Störk *et al.*, 2004; Dijk *et al.*, 2005; Mattace-Raso *et al.*, 2006; Ogawa *et al.*, 2009). Additionally, there is increasing scepticism of the usefulness of IMT as a risk stratification tool for the general population (Helfand *et al.*, 2009; Lorenz *et al.*, 2010; Simon *et al.*, 2010). Moreover, the decreased SV-to-PP ratio has been found to relate to cardiovascular risk and to predict cardiovascular events (de Simone *et al.*, 1999; Lind *et al.*, 2004, 2006), but whether SV predicts cardiovascular events has not been extensively investigated. Nevertheless, age has been shown to associate with LV remodelling accompanied by decreased SV, and this pattern of ventricular remodelling predisposes to greater cardiovascular risk (Cheng *et al.*, 2009). All in all, the ability of these indices of cardiovascular structure and function to predict cardiovascular risk is limited and, to a degree, controversial. It could therefore be of clinical interest to develop a cardiovascular parameter including information on several aspects of cardiovascular structure and function and thus possibly improve risk stratification. ATT could potentially represent this kind of marker of cardiovascular health, and future studies should hence address the relation between ATT and cardiovascular events.

A previous evaluation study has demonstrated that ICG reliably measures PWV between the aortic arch and popliteal artery when compared to the Doppler ultrasound method (Kööbi *et al.*, 2003). Moreover, previous studies have shown that ICG accurately measures cardiac output when compared with the thermodilution and direct Fick methods under different conditions (in the supine position, during a head-up tilt, after anaesthesia induction, after coronary bypass surgery) (Kööbi *et al.*, 1997a,b, 1999; Kaukinen *et al.*, 2003). Major advantages of the ICG method are the possibility to measure several systemic haemodynamic parameters simultaneously as well as its operator independence and the low cost of the equipment. Furthermore, because ICG automatically measures pulsatile changes in the arterial tree over the cardiac cycle, it provides a convenient method for measuring ATT in large-scale epidemiological studies.

The current study has some limitations. We examined the relationships between indices of arterial stiffness, subclinical atherosclerosis, cardiac pump function and ATT in a cross-sectional study, which cannot prove a causal relation between these measures. In addition, the study setting did not include prognostic data, and we were therefore not able to examine whether ATT predicts cardiovascular events or mortality. Finally, our population consisted of middle-aged and elderly Caucasians, limiting the generalization of the results.

In conclusion, the present study suggests that a new haemodynamic parameter known as ATT, reflecting the time difference between the onset of SV-induced arterial distension and maximal integrated arterial distension, could provide simultaneous information on arterial stiffness, subclinical atherosclerosis and cardiac pump function. Future longitudinal studies are required to determine whether ATT predicts cardiovascular events and mortality.

Acknowledgments

This study was financially supported by the University of Tampere and Tampere University Hospital Medical Funds.

Conflict of interest

None.

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ISBN 978-952-15-3760-8
ISSN 1459-2045