Physical activity and arterial stiffness in older adults of the SAPALDIA 3 cohort study

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List of Abbreviations

ADAM	Aggressive decrease of atherosclerosis modifiers
AIx	Augmentation index
baPWV	Brachial-ankle pulse wave velocity
CAVI	Cardio-ankle vascular index
CI	Confidence interval
cfPWV	Carotid-femoral pulse wave velocity
CVD	Cardiovascular disease
EVA	Early vascular ageing
IPAQ	International Physical Activity Questionnaire
MET	Metabolic equivalent
OR	Odds ratio
PWV	Pulse wave velocity
SAPALDIA	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults

Summary

Background

This PhD thesis presents the research work of the Swiss National Science Foundation (SNSF) funded project (#147022) entitled "Physical activity as a life style component of aggressive decrease of atherosclerotic modifiers (ADAM) in elderly subjects: the SAPALDIA Cohort Study." The study has been performed against the background that a physically active lifestyle is linked with decreased risk of cardiovascular disease (CVD) and CVD events, such as myocardial infarction or stroke, at all ages among others through improvements in arterial stiffness reflecting arterial remodeling. Arterial stiffness proved to be an independent predictor of all-cause and cardiovascular mortality. However, arterial stiffness in association with physical activity of different intensities has insufficiently been studied in Caucasian cohorts of older adults and not at all concerning the change of physical activity over time in older Caucasian adults.

Aims:

The research program realized the following aims: (1) evaluation of the measuring characteristics of the novel cardio-ankle vascular index (CAVI) and the brachial-ankle pulse wave velocity (baPWV) as marker of arterial stiffness for the first time in a Caucasian cohort of older adults and analyses of the (2) cross-sectional and (3) longitudinal association between physical activity as a preventive life style component of aggressive decrease of atherosclerotic modifiers and CVD assessed as arterial stiffness in this ageing Caucasian clientele.

Methods:

The PhD thesis comprised a large nested study of the second follow-up of the **S**wiss Cohort Study on **A**ir **P**ollution **a**nd **L**ung and Heart **D**iseases **i**n **A**dults (SAPALDIA 3) including 3026 participants aged 50-81 years. SAPALDIA is a multi-center cohort study in eight distinct areas

representative of the environmental diversity of Switzerland geared to the investigation of respiratory and cardiovascular health (including morbidity and mortality) in its ageing cohort. Mixed central and peripheral arterial stiffness was measured oscillometrically and simultaneously by CAVI and baPWV using a non-invasive VaSera VS-1500N vascular screening system (Fukuda Denshi, Tokyo, Japan). The self-reported International Physical Activity Questionnaire (IPAQ) long version was administered to classify the physical activity level in 3072 individuals for the cross-sectional analyses. The IPAQ long form asks for the frequency and duration of moderate and vigorous physical activity in different domains performed during the last seven days (leisure time, domestic and gardening activities, work-related, transport-related). Furthermore, we assessed physical activity in SAPALDIA 2 (2001-2003) and SAPALDIA 3 (2010-2011) using a short questionnaire with a cut-off of at least 150 minutes of moderate-to-vigorous physical activity per week for sufficient activity for the longitudinal analyses. We used multivariable mixed linear and logistic regression models adjusted for several potential confounders to analyze associations between physical activity and arterial stiffness.

Results:

Measuring characteristics of arterial stiffness indices (CAVI, baPWV)

The first aim was to determine the measuring characteristics in terms of the reproducibility of the novel arterial stiffness measure CAVI together with baPWV in a Caucasian clientele within the SAPALDIA cohort. These two arterial stiffness indices are derived from an oscillometric measurement with the VaSera VS-1500N vascular screening system. This work resulted in one publication showing the high reproducibility of these indices (Milestone 1).[1] This could be done for the first time in a Caucasian cohort, since both of these newly emerging arterial stiffness indices reflecting early CVD risk have so far mainly been studied in Asian populations or only in small studies with Caucasians. Valid markers of CVD are essential and highly important for CVD risk stratification on the population level. The analyses of the association of CAVI with blood pressure in comparison with baPWV has been conducted but could not been integrated in a publication so far. The association between CAVI and carotid intima media thickness as a traditional and well established marker of cardiovascular risk is pending. However, we have analyzed associations of CAVI and baPWV with age and sex as the main determinants of arterial stiffness in the SAPALDIA cohort proving the high quality of these indices.

Cross-sectional association of physical activity and arterial stiffness

In the next step, we have focused on the second aim targeting the analyses of the cross-sectional association between physical activity and arterial stiffness reflecting CVD risk in multilevel models including several confounding factors. Physical activity is regarded as an important health promotion measure with protective impact on the cardiovascular system and, thus, as one component of aggressive decrease of atherosclerotic modifiers. The main focus of the second aim was the question how a physically active lifestyle is cross-sectionally associated with arterial stiffness in the SAPALDIA cohort. Up-to-date this question has been insufficiently studied in older adults in population based studies. Furthermore, there is no comparable cohort in which a measure of arterial stiffness could be analyzed in association with a detailed questionnaire of physical activity like the IPAQ. During the data collection of SAPALDIA 3 the IPAQ has been consulted to classify the subjects' physical activity level. We hypothesized that a sedentary lifestyle is associated with increased arterial stiffness assessed by CAVI and baPWV. We found that in this general Caucasian population of older adults higher levels especially of vigorous physical activity were associated with lower arterial stiffness reflecting lower cardiovascular risk. These data support the importance of physical activity for improving cardiovascular health in older adults. These results are included in a manuscript published in the European Journal of Epidemiology (Milestone 2).[2]

Longitudinal association of physical activity and arterial stiffness

To add on this from a longitudinal point of view we have extensively worked on the third aim analyzing the association between change in physical activity between the first and second follow-up of SAPALDIA (SAPALDIA 2 to 3) and CVD risk using CAVI and baPWV as marker in multilevel models including several confounding factors. We hypothesized that an increase in physical activity between SAPALDIA 2 and 3 is associated with lower cardiovascular risk assessed by arterial stiffness. This is the first longitudinal population based cohort study showing that keeping up or adopting a physically active lifestyle was associated with lower arterial stiffness in older adults after a follow-up of almost a decade. Increasing the proportion of older adults adhering to physical activity recommendations incorporating also vigorous physical activity may have a considerable impact on vascular health at older age and may contribute to healthy ageing in general. These findings will strengthen physical activity recommendations within CVD prevention guidelines in older adults with respect to

the prevention of manifest CVD and related health outcomes. A manuscript presenting these findings have been published in the journal Age and Ageing (Milestone 3).[3]

Conclusions:

Consequently, the aims of the PhD research plan could be fulfilled within the proposed timeline, except the pending analyses of the association between CAVI and baPWV with carotid-intima media thickness. We could show that CAVI and baPWV are non-invasive arterial stiffness indices that are easy-to-apply and reproducible for population wide CVD risk stratification in Caucasians. Because arterial stiffness receives growing significance for examinations of asymptomatic subjects in research our cohort study results will lead to improvements of early stage diagnosis and treatment of CVD. Risk stratification is essential for goal-oriented and area-wide primary and secondary care. Early detection of CVD and cardiovascular risk factors is crucial besides promotion of prevention and early treatment for diminishing the increasing health and economic impact of CVD. CAVI and baPWV could be implemented in this epidemiological cohort study to assess the cardiovascular risk related to increased arterial stiffness and associated with insufficient physical activity. Besides, a long-term physically active lifestyle was shown to be beneficially associated with vascular ageing and therefore decreased CVD risk on the population level in the long-term. Since there are few population based studies in Caucasians concerning this topic and the growing acknowledgement of physical activity in population health interventions this study presents highly relevant and unique results in line with current epidemiological, medical and sports science research trends. In conclusion, physical activity may play a major role in long-term healthy cardiovascular ageing at the population level and should be emphasized in CVD management and prevention guidelines. Increasing the proportion of older adults adhering to physical activity recommendations incorporating also vigorous physical activity may have a considerable impact on vascular health at older age and may contribute to healthy ageing in general.

Chapter 1

Introduction

Chapter 1 Introduction

1.1 Physical Activity

1.1.1 Physical Activity Epidemiology in Adults

The current European Guidelines on cardiovascular disease prevention in clinical practice of the European Society of Cardiology[4] and global physical activity guidelines[5] recommend a minimum of 150 minutes per week of at least moderate intensity physical activity for adults to beneficially affect population health and cardiovascular mortality. Adherence to physical activity guidelines is suggested to reduce the mortality rate by 25%[6] and an increase of physical activity by 10% or 25% could prevent more than 533'000 or 1.3 million deaths, respectively, per year worldwide.[7] According to the 2013 Hypertension Guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) physical activity is one lifestyle measure of health promotion besides smoking cessation, weight reduction in the overweight, moderation of alcohol consumption and balanced diet concerning all populations.[8] Nevertheless, physical activity is underrepresented in the daily life of the majority of the worldwide population. As pointed out at by the Lancet Physical Activity Series 31.1% of the world population does not meet current physical activity recommendations.[9] In the US only 28% of women and 31% of men meet the current guidelines, and 41% of women and 39% of men are not physically active during their leisure time at all.[10] According to the Special Eurobarometer 412 of 2014 54% of the interviewed European Union citizens did not perform any vigorous physical activity in the previous week and 44% any moderate physical activity, respectively.[11] In this European survey 13% reported on no bouts of ten minutes walking in the past week at all. In other words, two thirds of Europeans do not meet current physical activity guidelines.[12] In Switzerland 72% (65% in 2007) of the population (69% in women and 76% in men) achieve at least 150 minutes of moderate intensity physical activity and, therefore, are sufficiently active according to the 2012 Swiss Health Survey.[13,14] One third of the Swiss population still has to be categorized as insufficiently active. However, as pointed out in the 2013 Health Enhancing Physical Activity Core Document this comparably high proportion of Swiss people being sufficiently active can be explained by the new physical activity guidelines that do not take into account the frequency of performed physical activity.[14] According to the former physical activity guidelines not only the amount of 150 minutes of moderate-to-vigorous physical

activity had to be fulfilled to be categorized as sufficiently active, but also a frequency of 3-5 of activities of at least 10 minutes had to performed throughout a week on a regular basis. The 24% irregularly active Swiss adults of the 2007 Swiss Health Survey would therefore also be insufficiently active according to the previous recommendations, amounting to a total of 59% insufficiently active Swiss adults in 2007 instead of 35%.

1.1.2 Health Benefits of Physical Activity

A physically active lifestyle is linked with decreased risk of cardiovascular disease (CVD) and CVD events, such as myocardial infarction or stroke, at all ages among others through improvements in arterial stiffness reflecting arterial remodeling.[15–18] Besides beneficial effects on CVD development and progression physical activity has been shown to be beneficially associated with the primary and secondary prevention of various diseases such as diabetes, cancer, hypertension, obesity, depression, dementia and osteoporosis.[19,20] In a recent cohort study in 334'161 European men and women it has been shown, that in the general population being at least moderately physically active compared to inactive reduces the number of deaths by 7.35% and would increase life expectancy at birth by 0.70 years.[21] These results were independent of body mass index and waist circumference. Comparably Wen et al. have found among 416'175 Taiwanese aged 20 years or older, that 15 minutes of daily moderate physical activity could decrease mortality risk by 14% and increase life expectancy by 3 years compared to inactive persons.[22] This suggests that a substantial public health benefit may arise from efforts to promote moderate-to-vigorous physical activity and to reduce physical inactivity.

1.1.3 Physical Inactivity

In contrast, physical inactivity is regarded as one of the main risk factors for both non-communicable diseases in general and CVD in particular.[23] Physical inactivity accounts for about 6% of all deaths worldwide and, thus, is the fourth leading risk factor for premature mortality.[24] According to the same report of the World Health Organization (WHO) physical inactivity is associated with around 1 million deaths per year in Europe. Physical inactivity has to be distinguished by sedentary behavior. According to the current definition sedentary behavior refers to activities with an energy expenditure of 1-1.5 metabolic equivalents (one MET is the energy cost of resting quietly, equivalent to an oxygen uptake of 3.5 mL*1/kg*1/min), namely especially sleeping, sitting, reclining or watching TV.[25] In contrast there are light physical activities with an energy expenditure of 1.6-2.9 METs such

as slow walking, sitting in combination with writing or cooking. Physically inactive are persons who are not meeting current physical activity guidelines and, thus, perform less than 150 minutes of moderate physical activity or an equivalent of 75 minutes of vigorous physical activity per week.[14,26]

Influences of the environment are supposed to be very important determinants for physical activity in a public health context.[27] These include influences such as the design of public spaces and parks, the nearness and availability of sports and retail facilities, and especially transport (roads, walking and cycling paths, subways) and occupation settings related to physical activity or sedentary behavior.[27] In the last decades with an increasing level of technology the environment has become less requiring of physically strenuous activities and less stimulating for being physically active at all. Likewise daily amounts of physical activity show a distinct decline, with increasing time spent being sedentary, especially sitting.[9] In the past ten years scientific knowledge has been accumulated presenting the adverse health effects of sedentary behavior, most often studied concerning daily sitting time.[28] In this context it has been shown, that time spent viewing television[29], time spent sitting in cars[30] or prolonged sitting in general[31] is associated with increased CVD and all-cause mortality. A recent systematic review came to the same conclusions summarizing that there is strong evidence for an association between sedentary behavior and all cause and CVD mortality.[32] This association has been shown to be independent of leisure time physical activity suggesting, that even complying with current physical activity recommendations cannot counterbalance the adverse health effects of prolonged sitting.[33] There is growing evidence that efforts to reduce prolonged sitting time, while increasing time being physically active have to be pursued in view of population health.[33,34] Up-to-date interventions are therefore targeting to reduce sitting bouts of more than 30 minutes such as within workplace settings.[35] On this scientific basis both prolonged sitting and too little moderate-to-vigorous physical activity have to be considered as separate risk factors for cardiovascular and other non-communicable diseases.[26]

1.2 Cardiovascular disease

Within the European Union 41% of all deaths in 2003 were explained by diseases of the circulatory system including ischemic (coronary) heart diseases, other heart diseases and cerebrovascular diseases.[36] Myocardial infarction and stroke as the main CVD are the first and second leading death causes worldwide and are solely responsible for one third of the

deaths in the world.[37,38] More than half of the deaths on account of non-communicable diseases (16.7 million of 32 million) are directly connected to CVD.[38] A recently published report of the American Heart Association highlighted that the prevalence rate for any form of CVD will increase to 40.5% of the US population and future costs of patients suffering from CVD will triple.[39] Therefore, CVD represents a major cause of morbidity and mortality and, hence, a major global health problem for both the society and the health care system. A recently observed decline in the rates of CVD mortality in developed countries is strongly attributed to improved treatment[37,40] and augmented attention to risk factor identification, stratification and modification especially regarding smoking cessation, physical exercise, and control of weight.[41] Obviously, the potential of lifestyle prevention has not exhausted its potential even though preventive approaches are still "undervalued and underused around the world" (p.657).[37] The progression of CVD is directly related to the long-term asymptomatic process of atherosclerosis, which often already begins in adolescence.[42] Atherosclerosis is the main form of arteriosclerosis, which comprises every arterial hardening and thickening.[43] According to the most common explanatory approaches atherosclerosis is an inflammatory process characterized by pathophysiological modifications of the endothelial layer.[43,44] Thereby, lipid and lipoprotein particles accumulate beneath the endothelium in the initial stage, by what immunoactive cells (peripheral blood monocytes and T-lymphocytes) are chemotactically attracted, move to the intima, where they result in the formation of fatty streaks.[44] If the traditional cardiovascular risk factors, such as high blood pressure, tobacco use, alcohol consumption, cholesterol, and obesity or overweight,[38] remain unchanged at this point, an atherosclerotic plaque (fibrous plaque, atheroma) as an accumulation of fibrous tissue, cells, and lipid originates from this first lesion of atherosclerosis.[44] In the case of fissures, erosion, ulceration or rupture because of "hemodynamic trauma, local attachment and activation of platelets and blood cells, inflammatory processes in the plaques, and cytotoxic effects of plaque contents" (p. 596)[45] the formation of an arterial thrombus and dynamic coronary vasoconstriction is likely to occur as starting points of further worsening.[46] This may lead to serious cardiovascular events such as angina pectoris, myocardial infarction, sudden cardiac death or chronic coronary heart disease, summed up by the clinical term coronary heart disease.[47]

The described atherosclerotic alterations impair the two functions of the arterial system both the conduit of blood to the periphery and the cushioning of the pulsatile blood-flow

into an almost smooth flow in the microcirculation,[48] in order to protect arterioles and capillaries from pressure-induced damages.[49] The structural and functional properties of the arteries in terms of compliance characteristics facilitate these functions. Already at an early stage of atherosclerosis the aorta and major arteries stiffen and steadily lose their elastic and distensible abilities.[50] From this it follows that atherosclerosis is closely related to arterial stiffness.[51,52] Especially in arterial regions with high shear stress one can find with higher probability stiffer vessels and more often atherosclerotic altered vascular walls.[53] Wang & Fitch state that this vascular stiffening process is associated with foam cell-induced medial thickening, elastin degradation, and endothelial dysfunction.[50] Finally, the impairment of the buffer capacity on account of the arterial stiffness may lead to elevated left ventricular afterload followed by left ventricular hypertrophy, heart insufficiency, worsening of coronary ischemia and an increased risk of stroke, dementia and renal failure due to damages of the microcirculation.[49,54] Thus, arterial stiffness is an early, subclinical sign of grave cardiovascular alterations and different techniques of diagnosis need to be elucidated and enhanced to accomplish an application-oriented basis of primary and secondary medical care and prevention.

1.3 Arterial Stiffness

Arterial stiffness is a generic term for structural and functional properties as well as alterations of the arterial vessel system.[54] Stiffness is inversely associated with compliance as "a change in volume or cross-sectional area for a given change in pressure" (p. 159)[49] and to distensibility as "a fractional change in volume or cross-sectional area for a given change in pressure"[49], wherefore arterial stiffness needs to be differentiated from these concepts. Within the current research perspective arterial stiffness is regarded as a structural biomarker for early vascular ageing signalizing increased cardiovascular risk.[55,56] The concept of early vascular ageing (EVA) recently proposed by Nilsson et al. shows that arterial stiffness as a structural biomarker of cardiovascular risk is more reliable and consistent over a long period of time compared to circulating biomarkers like C-reactive protein or homocysteine.[55] This is because arterial stiffness reflects the accumulated vascular damage over the lifespan.[57] Arterial stiffness strengthens the significance of cardiovascular risk stratification at an early stage and therefore improves the diagnosis, treatment and cessation of subclinical arteriosclerotic process.[55] This is needed to implement early stage interventions targeted at the vascular health summed up by the term aggressive decrease of

atherosclerosis modifiers (ADAM).[55] Arterial stiffness proved to be an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension[58] and demonstrated its significance for estimating CVD prognosis.[59] As reviewed by Safar, Levy and Struijker-Boudier arterial stiffness is a marker for increased CVD risk, including myocardial infarction, heart failure, and total mortality, as well as stroke, dementia, and renal disease.[60] In this regard a recent prospective cohort study has shown that aortic stiffness adds significant information to the prediction of cardiovascular events and to the risk stratification of populations at intermediate risk.[61] Thus, arterial stiffness is recognized as a surrogate end point for cardiovascular events.[15,62] Different non-invasive surrogate measures are known (pulse wave velocity, pulse pressure, pressure pulse waveform analysis) that are marker of arterial stiffness and the underlying cardiovascular risk.[63] In a very recent position paper by the European Society of Cardiology Working Group on peripheral circulation several vascular biomarkers have been scrutinized for their ability of being a surrogate end point of cardiovascular events.[56] The consensus was that carotid ultrasonography, ankle-brachial index and carotid-femoral pulse wave velocity (cfPWV) meet the most criteria, and brachial-ankle pulse wave velocity (baPWV), central hemodynamics/wave reflections and C-reactive protein at least part of the criteria.

PWV expresses the velocity of the pressure pulse wave that is generated by the systolic contraction of the left ventricle and spreads out along the arterial tree.[15] In the same manner as arterial stiffness, PWV correlates inversely with the distensibility of the arteries that is PWV increases in accordance with the stiffening of the vessels.[54] PWV is not only strongly dependent on age[64] but also linearly related to blood pressure.[15,65,66] Arterial stiffness increases non-linearly with age, especially detectable after the age of 55-60.[67] Out of this growing rigidity of the vessel walls results a distinct greater disproportion of systolic blood pressure and diastolic blood pressure in the elderly, leading to a curtailment of the significance of cardiovascular risk analyses using blood pressure measurements.[67] Thus, Benetos et al. state that pulse waveform and PWV analyses can be advantageous compared to common blood pressure assessment.[64]

Recent overview publications demonstrated that PWV > 10 m/s can be considered as cardiovascular hazardous and as target organ damage.[15,65,68] Therefore, in the current 2013 Hypertension Guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) compared to the 2007 Guidelines the threshold of cfPWV for an

abnormal, high-risk cardiovascular status has been changed from 12 m/s to 10 m/s.[8,69] This lower threshold for cfPWV takes into account that the true distance covered by the pulse wave is 20% shorter than measured superficially with a tape measure from the carotid to the femoral artery and this method has therefore been recently recommended by an expert consensus.[70] Especially in middle-aged and older adults travel distance measured superficially multiplied by 0.8 has been shown to result in a closer approximation to invasive aortic PWV compared with other travel distance estimations.[71,72]

PWV measurements vary depending on the vessel regions included. They can provide predictions about different regions of the vascular system and therefore have only limited significance concerning the vascular system on the whole. cfPWV is commonly acknowledged as the ´gold-standard´ method for assessing central/ aortic arterial stiffness.[15] The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) recommend cfPWV as a tool for the assessment of subclinical target organ damage.[69] Besides, measuring of baPWV is widespread applied in Japan.[68] Since baPWV has revealed a reliable correlation to left ventricular mass and diastolic function,[65,66,68,73] has proven a considerable high validity, reproducibility, and good correlation with aortic PWV,[74] baPWV also features a reasonable tool for clinical use. A recent systematic review and meta-analysis by Vlachopoulos et al. strengthens the predictive ability of baPWV regarding critical outcomes in 8169 participants with a mean follow-up of 3.6 years.[62] The authors highlight the good association of baPWV with cardiovascular events, cardiovascular mortality and all-cause mortality with pooled relative risks of 2.95, 5.36 and 2.45, respectively, comparing two groups of high versus low baPWV. Thereby an increase of 1 m/s in baPWV was associated with an increase of 12%, 13%, and 6% in total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively. However, none of these methods allow assessing arterial stiffness quantitatively and independently of blood pressure and the arterial segments included in the baPWV calculations are rather virtually derived, wherefore Vlachopoulos et al. prefer to use the term brachial-ankle elasticity index (baEI) than baPWV.[62]

1.4 Cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV)

To overcome these methodological problems Shirai et al.[75] and Yambe et al.[76] proposed the cardio-ankle vascular index (CAVI) for non-invasive stiffness assessment of the arterial tree including the aorta, femoral artery, popliteal and tibial artery by using a device based on a

convenient volume plethysmographic method. CAVI is methodologically based on the measurement of baPWV with improvements regarding the length calculation of the included vessels, the pulse wave propagation time and the correlation with blood pressure.[75] CAVI clearly reflects the arterial stiffness between the heart and the ankle, by precise determination of the time point of the systolic aortic valve opening.[75] CAVI and baPWV are combined estimates of the central and peripheral arterial stiffness, thus systemic arterial stiffness indices.[75,77] CAVI's great advantage compared with other arterial stiffness parameters like cfPWV and baPWV is the lower correlation with blood pressure on account of an inclusion of a mathematical relationship to the mechanical properties of the arterial wall and the stiffness parameter β.[78,79] In a Japanese study with 135 hemodialysis patients baPWV and CAVI have been compared concerning their association with cardiovascular outcome.[80] Thereby only the highest tertile of baPWV (≥16.6 m/s) was significantly associated with a lower survival rate and was a determinant of cardiovascular death. This could not be shown for CAVI, which should theoretically be advantageous in the prediction of cardiovascular outcomes. More data on the associations of CAVI with different cardiovascular events and mortality are still missing, owing to the fact that CAVI is rather new. However, it can be assumed that CAVI implies good correlations as shown by Vlachopoulos et al.[62] for baPWV due to the methodological connection of both methods. CAVI is compatible with the PWV method, however, CAVI is mathematically derived from a modification of Bramwell-Hill´s formula and a substitution in the stiffness parameter β, and is adjusted for blood pressure (Fig. 1).[75] CAVI is not only theoretically but also experimentally proven less dependent on blood pressure at the time of measurement and, therefore, may be more useful for the clinical assessment of arterial stiffness than PWV.[79,81–83] For example, the diabetes and non-diabetes subjects of the study of Ibata et al. passed through CAVI and baPWV evaluations directly after exercise stress tests vigorous enough to influence blood pressure, whereby only baPWV was affected by the changes in blood pressure.[81] The same effect could be shown when only CAVI remained unchanged during general anesthesia in contrast to a decrease of baPWV and systolic blood pressure.[84] Yambe et al. confirmed this superiority of CAVI over baPWV after heart transplantation, when CAVI remained stable whereas baPWV increased rapidly.[85] Different studies could demonstrate good reproducibility of CAVI as an index of both arterial stiffness and arterial distensibility without or distinct less dependency on blood pressure than PWV.[75,81,86–88] For this reason serial

examinations using CAVI as measurement of arterial stiffness are less affected by blood pressure fluctuations. This is especially important when measurements are done throughout the day like in the second follow-up of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA 3) because of known blood pressure variations and subsequent potential influences on PWV.

Stiffness Index β

$$\beta = \left(ln\frac{P_s}{P_D}\right)\left(\frac{D}{\Delta D}\right)$$

Bramwell-Hill equation

$$PWV^2 = \frac{\Delta P}{\rho} * \frac{V}{\Delta V} = \frac{\Delta P}{2\rho} * \frac{D}{\Delta D}$$

$$\frac{D}{\Delta D} = \frac{2\rho}{\Delta P} * PWV^2$$

CAVI

$$CAVI = a\left(2\rho * ln\frac{P_s}{P_D} * \frac{PWV^2}{\Delta P}\right) + b$$

Fig. 1. Deduction of CAVI from the stiffness index β and Bramwell-Hill's equation. PS-systolic blood pressure; PD-diastolic blood pressure; D-artery diameter; ΔD-change of artery diameter according to blood pressure; PWV-pulse wave velocity between the heart and the ankle; ΔP=PS-PD; ρ-blood density; a, b-constants; V-blood vessel volume; ΔV-change in blood vessel volume.

CAVI showed good reliability and reproducibility[86,89] with an interobserver correlation coefficient between 0.82 – 0.87 as reported by Wu et al.[90] and a coefficient of variation (3.8%) below the threshold for clinical useful testing in Asian populations.[75] However, there is lack of evidence concerning the reproducibility of CAVI and baPWV for arterial stiffness assessment in larger samples of Caucasians. Only one study with a small sample (n=7) showed a low variability of 2.9% expressed as coefficient of variation for CAVI on a week to week basis in Caucasians.[91] So far most of the published research results concerning CAVI and baPWV are from the Asian region, within which especially from Japan. Thus, the clinical and scientific evidence, usefulness and reference values of CAVI and baPWV need to be proven in representative Caucasian populations such as within the SAPALDIA 3 study.[56]

1.5 Physical Activity and Arterial Stiffness

Physical inactivity is one condition that is associated with increased arterial stiffness, and consequently with an increased risk of cardiovascular events.[15] The progression of CVD on account of insufficient physical activity is associated with long-term asymptomatic atherosclerotic processes that often already begin in adolescence with stiffening of the arteries.[42] Physical activity can be regarded as one component of aggressive decrease of atherosclerosis modifiers (ADAM).[55] Within the EVA-ADAM concept by Nilsson et al. early vascular ageing (EVA) is opposed by specifically targeted early stage interventions to positively influence the progression of cardiovascular risk associated with arteriosclerotic vessel modifications.[55] In recent years besides aerobic (endurance) exercise also resistance training has found its way into health guidelines as an elementary component.[92–94] Both

should be performed in a moderate intensity on a regularly, at the best daily basis.[69] Intervention studies with rather small sample sizes have demonstrated that arterial stiffness is modifiable by exercise training throughout life.[95,96] Generally one can state that the association between arterial stiffness and physical activity and exercise training depends on the type, duration, intensity and frequency of the respective physical activity. In this regard we could show in a recent systematic review of randomized controlled trials that aerobic exercise is beneficially associated with arterial stiffness especially when performed at higher intensities (see Appendix A).[95] In contrast, the results regarding resistance training are controversial ranging from negative to beneficial effects.[95–97]

Up to date there are only few population-based studies concerning physical activity and arterial stiffness. Aoyagi et al. examined the association of habitual physical activity (>3 metabolic equivalents; measured by step counts) and arterial stiffness in 198 women and men.[98] They reported on a beneficial effect of physical activity at least for the stiffening of central arteries. Hence they state that the more physical active a person is the lower the PWV values and, thus, less stiff the vessels are. This beneficial association of physical activity with arterial stiffness was recently confirmed by two large scale studies.[99,100] Thereby, higher walking speed was strongly associated with reduced cfPWV in older adults. In a population-wide study on 373 female and male Netherlands van der Laar et al. found that the effect of habitual physical activity depends on its intensity and differs with the respective arterial tree segment.[101] Accordingly, only vigorous but not light-to-moderate habitual physical activity provides favorable associations with compliance of peripheral arteries. In contrast, in one cross-sectional study in 538 healthy older adults longer time spent in light intensity physical activity was associated with lower cfPWV, independently of moderate-to-vigorous physical activity.[102] There is only one longitudinal study performed in 274 young overweight adults showing that an average increase in moderate-to-vigorous physical activity of 12.7 min/day is associated with reduced baPWV of at least 0.71 m/s.[77]

Arterial stiffness measured by CAVI and baPWV in association with physical activity of different intensities has insufficiently been studied in a Caucasian cohort of older adults and not at all concerning the change of physical activity over time in older Caucasian adults. SAPALDIA offers highly qualitative longitudinal cohort data in order to examine the association between short-term physical activity and change of physical activity over a period of almost a decade and markers of CVD like CAVI, baPWV, blood pressure, and

potential confounders. The association of the longitudinal physical activity from SAPALDIA 2 to SAPALDIA 3 may indicate whether long-term change of physical activity has an impact on arterial stiffness and, thus, may have consequences for promoting physical activity.

Chapter 2

PhD Thesis Aims and Hypotheses

Chapter 2 PhD Thesis Aims and Hypotheses

On the basis of the presented scientific background this PhD thesis has targeted the following aims:

- Aim 1: Determination of the measuring characteristics of oscillometrically measured arterial stiffness indices in a cohort of adults aged 50-81 years (SAPALDIA 3) in terms of analyses of the reproducibility of CAVI and baPWV (test-retest-reliability, age and sex association).
- Aim 2: Cross-sectional analyses of the association between physical activity assessed by the International Physical Activity Questionnaire (IPAQ) long version and CVD risk using CAVI and baPWV as arterial stiffness marker in multilevel models including several confounding factors.
- Aim 3: Longitudinal analyses of the association between change in physical activity between SAPALDIA 2 and SAPALDIA 3 and CVD risk using CAVI and baPWV as arterial stiffness marker in multilevel models including several confounding factors.

In view of these aims this PhD thesis focused on the evaluation of the following specific hypotheses:

- Hypothesis 1: CAVI and baPWV are reproducible measurements of arterial stiffness in a Caucasian cohort of adults aged 50-81 years.
- Hypothesis 2: A physically active lifestyle is beneficially associated with arterial stiffness in older adults and, therefore, with decreased cardiovascular risk independent of several potential confounding factors.
- Hypothesis 3: A long-term physically active lifestyle or the adoption of physical activity between SAPALDIA 2 and SAPALDIA 3 (almost a decade) is associated with lower cardiovascular risk assessed by arterial stiffness independent of several potential confounding factors.

Chapter 3

Methods

Chapter 3 Methods

3.1 Study Design and Population

The data were derived from SAPALDIA 3, the second follow-up of this multi-center cohort study in eight distinct areas representative of the environmental diversity of Switzerland targeted at the investigation of the effects of air pollution on respiratory and cardiovascular health including morbidity and mortality in its ageing cohort.[103,104] SAPALDIA is coordinated by the Swiss Tropical and Public Health Institute (Swiss TPH) in Basel (Principal Investigator Prof. N. Probst-Hensch) and has been funded by the Swiss National Science Foundation (SNSF) and the Federal Office of Environment for over 20 years. The first survey (SAPALDIA 1) of 9651 randomly selected adults, 18 to 60 years of age, started in 1991, and included a questionnaire, lung function and atopy tests. The same measurements were conducted in the first follow-up (SAPALDIA 2) in 2002 with 8047 subjects (86% of survivors) of which 65% underwent physical re-examination. SAPALDIA 3 was expanded by high relevance in chronic disease research and focused more precisely on cardiovascular health assessment. Thus, besides sonographic measurements of carotid-intima media thickness, PWV measurement was implied in 3025 subjects as a marker of arterial stiffness reflecting cardiovascular modifications and cardiovascular risk. SAPALDIA has earned high relevance in environmental and chronic disease research with more than 100 publications listed in PubMed. The respective Swiss cantonal ethical committees have granted ethical approval and participants gave written informed consent.

3.2 Physical Activity Assessment

For cross-sectional analyses the self-reported International Physical Activity Questionnaire (IPAQ) long version was administered to classify each subject's physical activity level.[105] The IPAQ long form asks for moderate and vigorous physical activity in different domains performed during the last seven days (leisure time physical activity, domestic and gardening activities, work-related physical activity, transport-related physical activity).[106] Moderate and vigorous intensities were associated with harder and much harder breathing, respectively. Total minutes per week of moderate physical activity (including walking), vigorous physical activity and total physical activity were calculated per domain and in total following the IPAQ guidelines.[106] They were weighted by their energy cost as metabolic equivalents (MET) with one MET equating to around one kcal/kg/hour, which approximately corresponds to sitting

quietly. This leads to a MET-minutes per week score reflecting total energy expenditure.[107] For longitudinal analyses a short self-reported physical activity questionnaire was administered within the SAPALDIA main questionnaire to classify the subjects' long-term physical activity from SAPALDIA 2 to SAPALDIA 3.[108] Thereby four questions were asked concerning the frequency and duration of physical activities per week.

- Do you participate in physical activities that make you a bit breathless; e.g. walking, dancing, gardening or other kinds of sport? How often do you participate in these activities each week?: Never/ Seldom/ 1 time a week/ 2 times a week/ 3 times a week/ 4 times a week/ 5 times a week/ 6 times a week/ 7 times a week.
- How long do you spend doing these activities each day? (minutes).
- How often do you usually exercise so much that you get out of breath or sweat? every day/ 4-6 times a week/ 2-3 times a week/ once a week/ once a month/ less than once a month/ never.
- How many hours a week do you usually exercise so much that you get out of breath or sweat? none/ about ½ hour/ about 1 hour/ about 2-3 hours/ about 4-6 hours/ 7 hours or more.

Physical activities with episodes of getting a bit out of breath were categorized as moderate intensity and physical activities linked with getting out of breath and sweating as vigorous intensity, respectively. We calculated minutes per week of moderate-to-vigorous physical activity, whereby minutes of vigorous physical activity were taken twice.[5] Subjects with less than 150 minutes of moderate-to-vigorous physical activity were categorized as insufficiently active (inactive), and subjects with at least 150 minutes as active, respectively, both in SAPALDIA 2 and SAPALDIA 3.[5]

3.3 Arterial Stiffness and Hemodynamics

Peripheral blood pressure and arterial stiffness was measured by means of the cardio-ankle vascular index (CAVI) and the brachial-ankle pulse wave velocity (baPWV) using a VaSera VS-1500 vascular screening system (Fukuda Denshi, Japan) (Fig. 2.).[75] CAVI is considered to be less dependent on the blood pressure at the time of measurement compared to common PWV measurements.[75] After resting for at least 10 minutes two measurements were taken at 3-5-min intervals in supine position and averaged for analyses. Common blood pressure cuffs were placed directly above each ankle and at each upper arm. ECG leads were attached at each wrist and a phonocardiogram on the sternal border in the second intercostal space to assess PWV by a foot-to-foot method and mathematically derive CAVI as described previously.[1]

On the basis of these peripheral recordings, pulse wave analysis will be performed retrospectively for future analyses using the ARCSolver algorithm (AIT Austrian Institute of Technology GmbH, Vienna, Austria) in order to derive aortic pulse wave velocity as a surrogate marker of aortic stiffness as well as central systolic and diastolic blood pressure within the first aim. The ARCSolver method is a mathematical procedure for the calculation of aortic stiffness and central hemodynamic measures from peripheral pulse waves and blood pressure measurements at the brachial artery using a common occlusive cuff.[109] We have recently proven the feasibility of this method in combination with the VaSera VS-1500 device in a separate study.[110]

Fig. 2. Arterial stiffness measured by means of the cardio-ankle vascular index (CAVI) and the brachial-ankle pulse wave velocity (baPWV) with blood pressure cuffs at each upper arm and above each ankle, ECG leads at each wrist and a phonocardiogram on the sternal border in the second intercostal space using a VaSera VS-1500 vascular screening system (Fukuda Denshi, Japan).

3.4 Covariates

Within SAPALDIA a broad range of possible covariates was available, such as detailed information on respiratory and cardiovascular health symptoms, doctor diagnosed diseases (e.g. cardiopulmonary and metabolic disease), anthropometric and socio-demographic characteristics, occupation, medication, smoking habits, and nutrition, either directly measured or assessed with questionnaires.

3.5 Statistical Analyses

For the analyses of aim 1 reproducibility of the respective arterial stiffness indices was assessed in a representative subsample (N=105) of the SAPALDIA 3 cohort. Thus, arterial stiffness was measured twice at 3-5 min intervals on each of two separate days within 3 months. Means of individual between-visit coefficients of variation and intraclass correlation coefficients using one-way analysis of variance were applied for statistical analyses. Mixed linear models were used to produce detailed information on the sources of variability of repeated arterial stiffness measurements including a fixed effect of time and random effects of subject, measurement day within subject, and fieldworker. We used Bland-Altman plots for graphical analyses.[111]

We used mixed linear and logistic regression models as appropriate, with a random study area effect to account for the multi-center setting for the cross-sectional and longitudinal analyses of aim 2 & 3. Based on the literature and previous analyses in this cohort we pre-selected potential confounding covariates. Covariates were considered as potential confounders if the p-value of their association with the respective outcome was <0.2. On the basis of prior knowledge a set of possible interaction terms between physical activity, age, sex and mean arterial pressure was tested to include in the final models. All identified covariates and interactions were added incrementally to the final model. For the cross-sectional analyses 1908 individuals of the SAPALDIA 3 cohort with complete datasets of arterial stiffness, IPAQ and the covariates of interest were available and included in the analyses. Comparisons of the variables of interest by physical activity levels were performed by using t tests, nonparametric median tests (Kruskal Wallis test) or $\chi 2$ tests, as appropriate, age associations by linear regression and sex differences by t-tests or non-parametric Wilcoxon-Mann-Whitney tests. We analyzed the association between long-term change in physical activity from SAPALDIA 2 to SAPALDIA 3 and arterial stiffness in SAPALDIA 3 in 2605 individuals with information on all variables of interest. All statistical analyses were performed using the statistical software Stata (StataCorp LP, USA) with $P < 0.05$ defining statistical significance.

3.5.1 Power Analysis

The power analyses have been performed with respect to CAVI as arterial stiffness outcome.

3.5.1.1 Reproducibility of Oscillometrically Measured Arterial Stiffness Indices

For the analysis of the reproducibility of CAVI and baPWV we calculated the coefficient of variation, expressing the standard deviation as a percentage of the mean, based on measurements which are either taken in the same session (intra-session variability) or between two sessions within 90 days (inter-session variability). A coefficient of variation below 5% is assumed to be acceptable for clinical purposes.[88] Furthermore, the intraclass correlation coefficient has been calculated, which reflects the proportion of the total variance that is due to the true variance among subjects. Based on Asian reproducibility studies we could assume the intraclass correlation coefficient of CAVI to be around 0.8.[75,86,88] Besides, there is only one study in Caucasians with a small sample of seven healthy volunteers aged 28.8 ± 5.1 years showing a low variability of 2.9% expressed as coefficient of variation for CAVI on a week-to-week basis.[91] In our reproducibility study, 105 subjects were measured twice, 90 days apart. Taking these factors into account, the 95%-confidence intervals for our reproducibility analysis has been assumed to be narrow (95%-CI 0.725-0.86). Thus, this reproducibility analysis could produce a precise estimate of the true intraclass correlation coefficient.

3.5.1.2 Association of Arterial Stiffness With Different Levels of Physical Activity

We classified our study population according to three physical activity levels (low, medium, high) based on the IPAQ data. We could assume the distribution of physical activity levels to be similar to the one in a previous study with the SAPALDIA sample by Felber Dietrich et al., where 42% were categorized as having low, 33% as having medium and 22% as having high physical activity.[112] Besides, the standard deviation of CAVI as the main outcome for these power analyses has been shown to be around 0.8.[113] Under the given assumptions we estimated to have sufficient power (80%) to statistically detect, at the usual significance level of 5%, a slight average effect of physical activity on CAVI of 0.05 per additional physical activity level. If 50% of the variance in physical activity were explained by confounder variables, we estimated to be able to detect an average effect of 0.08 per level of activity with the same power.

3.5.1.3 Association of Arterial Stiffness With Change in Physical Activity Between SAPALDIA 2 and 3

For the analysis of the association of arterial stiffness with change in physical activity the participant's change of physical activity from SAPALDIA 2 to 3 was categorized as follows: a) as remaining inactive if the participant was inactive in both assessments, b) as becoming inactive if active in SAPALDIA 2 but inactive in SAPALDIA 3, c) as becoming active if inactive in SAPALDIA 2 but active in SAPALDIA 3, and d) as remaining active if active in SAPALDIA 2 & 3. Based on repeated surveys in the Swiss household panel, we assumed the distribution of the four groups to be remaining inactive: 30%, becoming inactive: 20%; becoming active: 20%, remaining active: 30%.[13,14] As an example, we calculated the power for the comparison of the most extreme groups (remaining inactive vs. remaining active). With a standard deviation of CAVI of 0.8[113] and an overall N=3000 we calculated to be able to statistically detect, at the usual significance level of 5% and with a power of 80%, a clinically small difference of 0.11 between the mean values of CAVI of these two extreme groups. This also shows that the study population of this PhD thesis was large enough for comparisons between subgroups.

Chapter 4

Publication 1: Reproducibility of Arterial Stiffness Indices

This manuscript has been published in the Scandinavian Journal of Clinical and Laboratory Investigation. The final publication is available at http://informahealthcare.com/doi/abs/10.3109/00365513.2014.993692.

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ORIGINAL ARTICLE

Reproducibility of oscillometrically measured arterial stiffness indices: Results of the SAPALDIA 3 cohort study

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Abstract

Background. There is an increasing interest in oscillometric arterial stiffness measurement for cardiovascular risk stratification. We assessed reproducibility of the cuff-based arterial stiffness measures cardio-ankle vascular index (CAVI), brachial-ankle pulse wave velocity (baPWV) and peripheral augmentation index (pAI) in a subsample of the second follow-up of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA 3). ***Methods.*** CAVI, baPWV and pAI were measured twice within 90 days in a representative subsample ($n = 105$) of SAPALDIA 3 with a mean age of 63 years (52.4% female). ***Results.*** The mean coefficient of variation for CAVI was 4.4%, baPWV 3.9%, and pAI 7.4%. The intraclass correlation coefficient ranged from 0.6 for pAI to 0.8 for CAVI, and 0.9 for baPWV. The mixed linear model revealed that 68.7%/80.1%/55.0% of the CAVI/baPWV/pAI variance was accounted for by the subject, 5.2%/8.1%/<0.01% by the fieldworker, 6.7%/7.8%/28.5% by variation between measurement days, and 19.4%/4%/16.5% by measurement error. Bland-Altman plots showed no particular dispersion patterns except for pAI. ***Conclusions.*** Oscillometric arterial stiffness measurement by CAVI and baPWV has proved to be highly reproducible in Caucasians. Results of the pAI showed lower reproducibility. CAVI and baPWV can be implemented as easy-to-apply arterial stiffness measures in population wide cardiovascular risk assessment in Caucasians.

Key Words: *Cardiovascular disease, oscillometry, pulse wave analysis, reproducibility, vascular stiffness*

Introduction

There is an increasing scientific interest in oscillometric arterial stiffness measurement for cardiovascular risk stratification due to its easier methodology compared to ultrasonography and applanation tonometry. Arterial stiffness is an important predictor of cardiovascular disease, events, mortality and morbidity, and total mortality [1]. Arterial stiffness reflects the true damage on the arterial wall on account of several cardiovascular risk factors [2]. In contrast to classical biomarkers like mean arterial pressure or glycaemia, arterial stiffness does not fluctuate over the age range, but is increasing continuously instead [2].

The 'gold-standard' for measuring arterial stiffness non-invasively is the carotid-femoral PWV [1]. Applanation tonometry is the most widely used method to assess carotid-femoral PWV. Here the pulse waveform is obtained by measuring the blood pressure locally at the carotid artery and at the femoral artery with a tonometer. However, tonometric methods of assessing arterial stiffness are highly dependent on the quality of the measurement associated with the observer's skills based on extensive measurement training [3]. Valid arterial stiffness measures are needed for large clinical trials, as well as for daily clinical use that are highly reproducible to give a meaningful prediction of the underlying cardiovascular risk at an early stage.

The reproducibility and validity of the oscillometrically measured arterial stiffness indices

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cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV) has not been shown in Caucasian populations. Several studies on Asian populations have proven CAVI's clinical usefulness [4–15] and reproducibility [4,16–18] in healthy persons and patients. CAVI has been shown to be less affected by blood pressure at the time of measurement compared to baPWV [19]. There are also several Asian studies showing clinical associations of baPWV with CV risk factors and cardiovascular disease, as well as baPWV as a predictor of future cardiovascular events, mortality and subclinical target organ damage [20]. A meta-analysis summarized that an increase in baPWV by 1 m/s is associated with a 13% risk increase of cardiovascular mortality [20]. However, there is lack of evidence concerning the reproducibility of CAVI and baPWV for arterial stiffness assessment in larger samples of Caucasians. Only one study with a small sample ($n = 7$) showed a low variability of 2.9% expressed as coefficient of variation (CV) for CAVI on a week-to-week basis in Caucasians [18]. Therefore we analyzed the clinical reproducibility of the arterial stiffness indices CAVI, baPWV and peripheral augmentation index (pAI) obtained simultaneously based on a blood-cuff method in a larger study population of Caucasian individuals participating in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).

Material and methods

Study design and subjects

SAPALDIA is a multi-center cohort study with eight distinct geographic areas covering the environmental and demographic diversity of Switzerland (Aarau, Basel, Davos, Genève, Lugano, Montana, Payerne, Wald) [23,24]. SAPALDIA was initiated in 1991 to investigate the association of air pollution and lung diseases among randomly selected adults (18–60 years, $n = 9651$). The second follow-up (SAPALDIA 3) focuses more precisely on cardiovascular health assessment. Thus, besides sonographic measurement of the carotid-intima media thickness (CIMT) [25–27], the CAVI, baPWV and pAI were assessed as early arterial stiffness and atherosclerosis markers. Data collection was finished in 2011. The respective Swiss cantonal ethical committees have granted ethical approval. Participants gave written informed consent to participate in the study.

Arterial stiffness measurement

Arterial stiffness by CAVI, baPWV and pAI was measured in 3025 subjects of the SAPALDIA 3 cohort. In a representative subsample ($n = 105$) of SAPALDIA 3, we assessed reproducibility of these three non-invasive oscillometric arterial stiffness indices. We measured arterial stiffness twice at 3–5 min intervals on each of two separate days within 3 months (Figure 1).

CAVI, baPWV, and pAI were measured simultaneously using a VaSera VS-1500N vascular screening system (Fukuda Denshi, Tokyo, Japan) with the study participant being in supine position after 15 min of rest. The underlying methodology was extensively explained elsewhere [4]. CAVI and baPWV are directly associated with the stiffness of the arteries and cardiovascular risk. Blood cuffs were placed at each upper arm and above each ankle. The cuffs were kept at 30–50 mmHg to reduce the effect of cuff pressure. Electrocardiogram leads at each wrist and a phonocardiogram on the sternal border in the second intercostal space were applied to detect the initial notch of the pulse wave at the heart and the ankle. Thereby the time delay of the pulse wave from the heart to the ankle was determined by a foot-to-foot-method as the sum of the difference between the transmission time of the pulse waves to the brachium and the transmission time of the same waves to the ankle, and the time difference between the second heart sound on the phonocardiogram and the notch of the brachial pulse wave [12,16,28]. Vascular length (L) between the heart valve and the ankle artery is indirectly calculated from the individual height of the patient using the formula:

$L = 0.77685 \times \text{height} - 1.7536$ [cm] (according to the manufacturer).

The PWV is calculated by dividing the arterial length by the time delay of the pulse wave. CAVI is then mathematically derived from Bramwell-Hill's equation and the stiffness parameter ß with an inclusion of the PWV.

The pAI of the VaSera VS-1500N device is calculated as the ratio between the systolic pressures at the peak of the tidal wave and the peak of the percussion wave obtained from the right brachial pulse wave (according to the operation manual from the

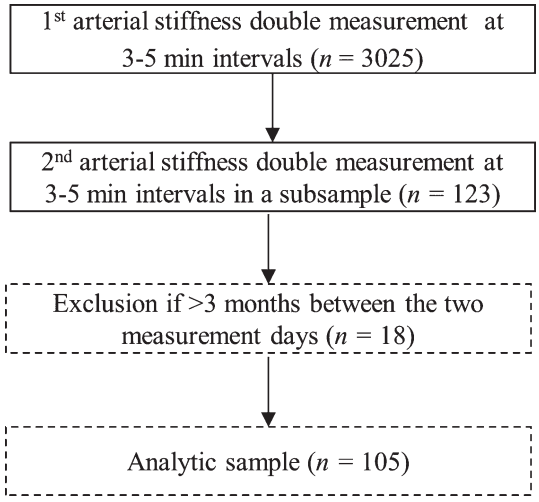

Figure 1. Study flow chart.

manufacturer, Ver.04). Therefore the obtained pAI reflects the ratio of the second pressure wave peak to the first assessed from the right brachial artery expressed in percent. That is to say that pAI stands for the augmentation of the pressure pulse that occurs due to reflections of the forward travelling pulse wave at sites of impedance changes in the periphery [29].

Statistical analyses

The reproducibility analyses included means of individual between-visit coefficients of variation (CV) and intraclass correlation coefficients (ICC) using one-way analysis of variance. Mixed linear models were applied to produce detailed information on the sources of variability of repeated CAVI, baPWV and pAI measurements. The models included a fixed effect of time and random effects of subject, measurement day within subject, and fieldworker. We used Bland-Altman plots (BAP) for graphical analyses [30]. For regression analyses, outcome data were averaged between left and right, separately for each of the two measurement time points of each day. For other analyses, averages were taken over all measurements of the respective day. All statistical analyses were performed using the statistical software STATA (StataCorp LP, Release 12, TX, USA); $p = 0.05$ was regarded as significance level.

Results

This randomly selected and representative subsample of the SAPALDIA 3 cohort study included 105 subjects with a mean age of 63 years, an age range of 50–79 years and a mean body mass index of 25.5 (standard deviation [SD], 4.1) kg/m^2. 55 (52.4%) subjects were female. The mean systolic blood pressure was 130.1 (12.9) mmHg and the mean diastolic blood pressure 80.0 (8.4) mmHg.

The mean of individual CVs of repeated CAVI measurements was 4.4%, of baPWV 3.9% and of pAI 7.4%. The ICC ranged from 0.6 for pAI to 0.9 for baPWV (Table I). The mixed linear model revealed that the subject accounts for 68.7% of the unexplained CAVI variance (80.1% baPWV, 55.0% pAI), measurement day within subject for 6.7% and the fieldworker for 5.2%. Residual variance accounted for 19.4% in the CAVI model, 4.0% for baPWV and 16.5% for pAI.

The BAP (Figure 2) of repeated CAVI measurements relates the individual CAVI differences between the two measurement days to the respective individual means. The mean differences with 95% confidence intervals (CI) in percent of the respective mean were for CAVI 1.7% (CI: 0.2%, 3.2%), for baPWV 0.9% (CI: −0.4%, 2.3%) and for pAI 0.7% (CI: −2.2%, 3.5%). The mean CAVI difference between the two measurement days was statistically significant ($p = 0.02$), but neither the baPWV difference ($p = 0.14$) nor the pAI difference ($p = 0.52$) was significant. The CAVI and baPWV BAP showed homogeneous scatter of individual differences within limits of agreement displaying the interval of 1.96 SD of the measurement differences either side of the mean difference in percent of the mean of −13.7% to 17.1% for CAVI and −13.1% to 15.0% for baPWV. The pAI BAP tended to heterogeneous scatter with higher pAI values at the second measurement day with increasing pAI means. Table II shows the means of each measurement day, mean differences and limits of agreement.

Discussion

The main study result shows that the oscillometrically measured arterial stiffness indices CAVI and baPWV are highly reproducible in Caucasians in a cohort setting. The methodology is applicable for large clinical trials or cohort studies. The simultaneously assessed pAI of the VaSera VS-1500N device of Fukuda Denshi (Tokyo, Japan) shows lower reproducibility.

A CV of less than 5% is commonly regarded as threshold for clinical useful testing in medicine [17]. Our mean CVs of CAVI and baPWV were below this threshold indicating high reproducibility and applicability of CAVI and baPWV for arterial stiffness measurement in Caucasians. Our reproducibility

Table I. Intraclass correlation coefficients (ICC) and mean coefficient of variation (CV) with 95% confidence interval (CI) and percent variance explained by the factors subject, measurement day within subject, fieldworker and by the residuals.

	ICC (95% CI)	Mean CV [%] (95% CI)	Variance [%] explained by			Unexplained variance [%]
			subject	measurement day	fieldworker	
CAVI	0.80 (0.73–0.87)	4.38 (3.67–5.09)	68.71	6.71	5.21	19.37
baPWV [m/s]	0.90 (0.87–0.94)	3.88 (3.32–4.44)	80.13	7.84	8.08	3.95
pAI	0.59 (0.47–0.72)	7.35 (6.13–8.56)	55.03	28.47	< 0.01	16.50
SBP [mmHg]	0.69 (0.59–0.79)	4.40 (3.64–5.16)	64.13	22.48	4.75	8.64
DBP [mmHg]	0.70 (0.61–0.80)	4.72 (3.94–5.51)	66.65	20.57	3.30	9.48

CAVI, Cardio-ankle vascular index; baPWV, brachial-ankle pulse wave velocity; pAI, peripheral augmentation index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

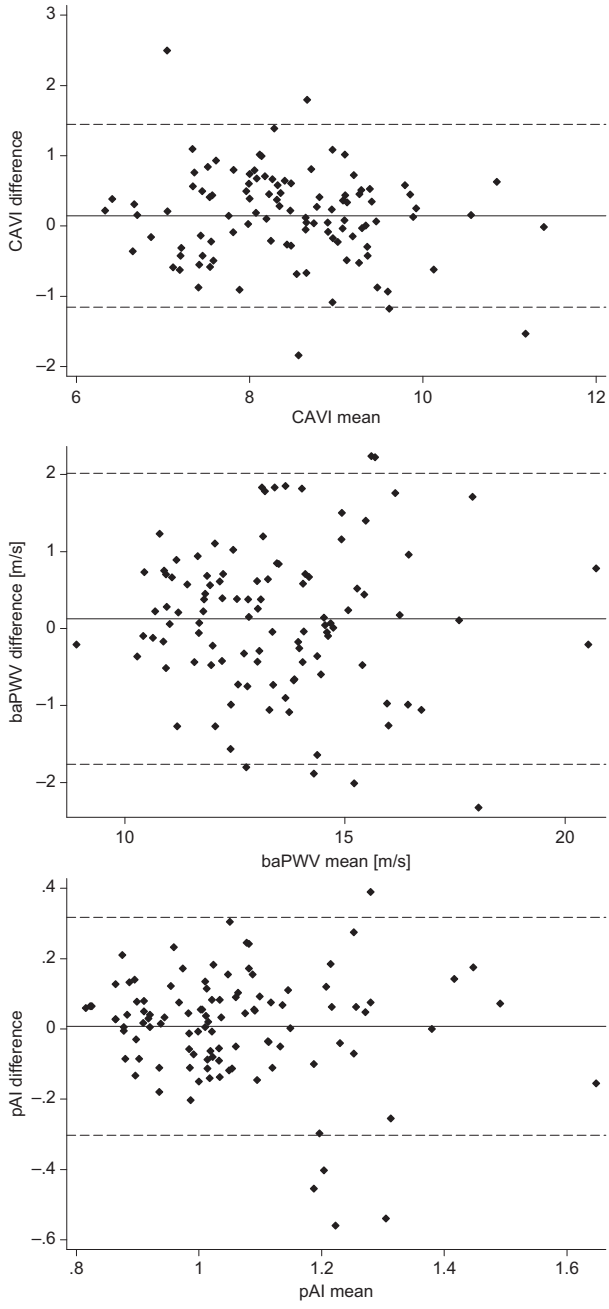

Figure 2. Bland-Altman plots of arterial stiffness indices cardio-ankle vascular index (CAVI), brachial-ankle pulse wave velocity (baPWV) and peripheral augmentation index (pAI) at two different measurement days with mean difference as thin black line and limits of agreement (mean [2SD]) as dashed black lines.

analyses by mean CV and BAP are consistent with findings in Asian populations, both in healthy subjects [4] and patients [17]. This is the case even though our validation sample was far larger, which could increase the variability. The only study in a very small Caucasian sample ($n = 7$) showed a week to week CV of 2.9% [18]. In addition to CV, the most commonly used statistical measure of reproducibility, we used ICCs, mixed linear regression models and BAPs to overcome drawbacks of single methods and to confirm the statistical analyses as recommended [31].

The CV results are strengthened by the very good ICCs of 0.8 for CAVI and 0.9 for baPWV, respectively. The ICC quantifies reproducibility of repeated measurements by reflecting the proportion of the total variability that is attributable to the subject [32]. The high proportion of variance on account of the subject within the mixed model (CAVI, 68.7%; baPWV, 80.1%) is in line with the high ICC value. It shows that most of the measurement variance of these indices is due to subject specific characteristics. Since the calculation of the ICC is not accounting for covariates like fieldworker or measurement day within subject, the ICCs are slightly higher. Here the variances of the covariates accounted for in the mixed model are attributed to the subject. The comparably high unexplained variance in the model for CAVI of 19.4% and for pAI of 16.5% (baPWV, 4.0%) signals that there is still a considerable amount of uncertainty connected with the statistical modelling of CAVI and pAI. In addition the regression analyses show that the fieldworker effect is small with 5.2% of the CAVI variance and 8.1% of baPWV. CAVI and baPWV measurement involves basic clinical devices (blood cuffs, electrocardiogram leads, phonocardiogram), which makes it easily applicable. Our data show that CAVI and baPWV measurement with the VaSera VS-1500N screening system has limited need for fieldworker training in a standardized setting. The significant CAVI difference of 0.15 between the first and second measurement relates to a proportion of only 1.7% of the CAVI mean and only 15% of the CAVI SD. From a clinical point of view this difference can be regarded as non-relevant, since the difference is much less than half of one SD [33].

Table II. Mean and standard deviation (SD) of CAVI, baPWV and pAI of each measurement day (1st/2nd).

	1st mean (SD)	2nd mean (SD)	Mean difference (CI) [%]	LoA [%]
CAVI	8.52 (1.01)	8.38 (1.10)	1.72 (0.22–3.21)	− 13.67; 17.10
baPWV [m/s]	13.48 (2.13)	13.36 (2.14)	0.94 (− 0.42–2.30)	− 13.13; 15.00
pAI	1.06 (0.16)	1.05 (0.18)	0.66 (− 2.17–3.50)	− 28.58; 29.91
SBP [mmHg]	131.81 (15.06)	128.34 (12.64)	2.67 (1.10–4.24)	− 13.54; 18.89
DBP [mmHg]	81.11 (9.42)	78.90 (8.63)	2.77 (1.16–4.39)	− 13.89; 19.34

CAVI, Cardio-ankle vascular index; baPWV, brachial-ankle pulse wave velocity; pAI, peripheral augmentation index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LoA, limits of agreement.

This statistical significance does not affect the very good CAVI reproducibility.

BAP is the accepted method for reproducibility testing of a new measurement in medical science graphically [31]. Kubozono et al. measured CAVI in 21 Japanese twice within two weeks [16]. Both their relative mean CAVI difference (2.4%) and their BAP limits of agreement in percent from the mean from − 14.4% to 20.5% were comparable to our study results. The Pearson correlation between the two measurements was very strong indeed ($r = 0.93$, $p < 0.0001$). However, the Pearson correlation coefficient is not a sufficient measure of reproducibility [30,31]. Linear correlation does not account for systematic bias in the mean or the dispersion of two related measurements nor for differences in scale. It is a measure of the strength of linear association of two variables rather than of the agreement between two measurements [34].

The pAI assessed with the VaSera VS-1500N device reveals a distinct lower reproducibility than CAVI and baPWV. With an ICC of 0.6, a CV above 5% (7.4%) and the subject accounting for only 55.0% of the total measurement variance all of the reproducibility measures of pAI ranged below the results of CAVI and baPWV. Furthermore, the pAI BAP showed an inhomogeneous scatter with increasing pAI means and broader limits of agreement. In contrast to the central augmentation index used generally [35], the pAI given by the VaSera VS-1500N device reflects vascular stiffness assessed peripherally from the right brachial pulse wave (according to the operation manual of the manufacturer, Ver.04, p. 14–6). It can be hypothesized that the difference in reproducibility between the three indices is related to the variation in the included vessel segments. It has also clearly been shown that the augmentation index is affected by heart rate variation resulting in considerable short-term changes [36]. This may also negatively impact on the pAI reproducibility. There is no ongoing study using the pAI of the VaSera device for pulse wave analyses to our knowledge. However, it has been shown that pAI is closely related to central AI because of the strong link between the late systolic peak and central systolic blood pressure [29]. Therefore, pAI may have further prognostic and therapeutic potential concerning central hemodynamics [29]. More research on this pAI is needed to investigate its validity for future clinical use and cardiovascular investigations.

The strength of this study is the large representative reproducibility sample, as well as the extensive statistical measures investigated. For the first time the reproducibility of the arterial stiffness indices CAVI and baPWV is analyzed in a larger Caucasian sample. The data are derived from a population-based cohort and each measurement is conducted in concordance with a detailed protocol. Furthermore, for the purpose of such a methodological study a large sample ($n = 105$) was analyzed compared to other reproducibility studies ($n = 7$–35) [4,16–18,37]. Up to date the carotid to femoral (aortic) PWV is still considered the 'gold-standard' for arterial stiffness assessment [1]. This measurement has proven good reproducibility [37], but has major drawbacks in terms of substantial need in fieldworker training and concerning the sensitivity of the measuring site at the femoral artery [38]. A limitation of our study is the lacking internal comparison with another method. However, a previous study showed that carotid-femoral PWV assessed with the SphygmoCor device (AtCor, Medical Pty Ltd, Sydney, Australia) had a nearly twice as high intra-session variability expressed as CV (6.1% vs. 3.2%) than for CAVI in Caucasians [18].

Conclusions

In summary, this study has proven good reproducibility of the non-invasive, cuff-based arterial stiffness indices CAVI and baPWV in a subsample of a Caucasian cohort. CAVI measurement is based on the easy-to-apply oscillometric measurement of the baPWV. Results of the pAI derived from the VaSera VS-1500N vascular screening system demonstrated to be less reproducible. The reasons for this finding need further investigation. CAVI and baPWV are highly suitable and recommendable for population wide studies or cardiovascular risk assessment and surveillance on the individual and population level in Caucasians.

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Appendix

Current Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) Team

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Key: (a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics.

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Chapter 5

Publication 2: Cross-sectional Physical Activity & Arterial Stiffness

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PHYSICAL ACTIVITY

Physical activity is associated with lower arterial stiffness in older adults: results of the SAPALDIA 3 Cohort Study

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Abstract Associations of physical activity (PA) intensity with arterial stiffness in older adults at the population level are insufficiently studied. We examined cross-sectional associations of self-reported PA intensities with arterial stiffness in elderly Caucasians of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. Mixed central and peripheral arterial stiffness was measured oscillometrically by the cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV). The self-reported International Physical Activity Questionnaire long version was administered to classify each subject's PA level. We used univariable and multivariable mixed linear and logistic regression models for analyses in 1908 persons aged 50 years and older. After adjustment for several confounders moderate, vigorous and total PA were inversely associated with CAVI ($p = 0.02$–0.03). BaPWV showed negative and marginally significant associations with vigorous and moderate PA (each $p = 0.06$), but not with total PA ($p = 0.28$). Increased arterial stiffness (CAVI ≥ 9, upper tertile) was inversely and significantly associated with vigorous PA [odds ratio (OR) 0.65, 95 % confidence interval (CI) 0.48–0.88], and marginally significantly with total PA (OR 0.76, 95 % CI 0.57–1.02) and moderate PA (OR 0.75, 95 % CI 0.56–1.01). The odds ratio for baPWV ≥ 14.4 was 0.67 (95 % CI 0.48–0.93) across the vigorous PA levels, and was non-significant across the total (OR 0.91, 95 % CI 0.66–1.23) and moderate PA levels (OR 0.94, 95 % CI 0.69–1.28). In this general Caucasian population of older adults higher levels especially of vigorous PA were associated with lower arterial stiffness. These data support the importance of PA for improving cardiovascular health in elderly people.

Keywords Arterial stiffness · Cardiovascular disease prevention · Epidemiology · Physical exercise · Prevention

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Background

Physical inactivity is regarded as one of the main risk factors for both non-communicable diseases in general and cardiovascular diseases in particular [1]. 6 % of the burden of disease from coronary heart disease and 9 % of premature deaths worldwide in 2008 are attributable to physical inactivity [2]. Adherence to physical activity (PA) guidelines is suggested to reduce the mortality rate by 25 % [3] and an increase of PA by 10 or 25 % could

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prevent more than 533,000 or 1.3 million deaths, respectively, per year worldwide [2]. A physically active lifestyle is linked with decreased risk of cardiovascular diseases and events at all ages through improvements in arterial stiffness reflecting arterial remodeling [4–6]. Arterial stiffness is a reversible, non-invasive structural biomarker of potentially grave cardiovascular modifications and is independently associated with cardiovascular disease and events [7, 8]. Stiffening of the arteries is closely linked with ageing related elastin degeneration and collagen proliferation reflecting vascular ageing [9].

The current European Guidelines on cardiovascular disease prevention in clinical practice of the European Society of Cardiology [10] and PA guidelines [11] recommend a minimum of 150 min per week of at least moderate intensity for adults to beneficially impact on the population health and cardiovascular mortality. However, in larger samples associations between PA intensities and arterial stiffness have so far mainly been analyzed regarding central arterial stiffness in adolescents and middle-aged persons [12–15]. In two population based studies of older adults walking speed was inversely associated with central arterial stiffness [16, 17]. Besides, there are only two medium sized cross-sectional studies showing that PAs of different intensities are associated with lower central arterial stiffness in older adults [18, 19].

The cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV) are mixed measures of central and peripheral arterial stiffness that have mainly been studied in Asian populations so far [20, 21]. There are no data on the population level in older adults of the association between different intensities of PA and arterial stiffness measured by CAVI and baPWV. Therefore, we examined associations of self-reported PA intensities with these arterial stiffness indices in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).

Methods

Study design and participants

SAPALDIA 3 is the second follow-up assessment of an ongoing multi-center cohort study including eight distinct rural and urban areas which represent the environmental and demographic diversity of Switzerland (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, Wald) [22, 23]. SAPALDIA was initiated in 1991 to investigate the association of air pollution and lung diseases among randomly selected adults (18–60 years, N = 9651). SAPALDIA 3 additionally focused on cardiovascular health assessment and arterial stiffness was measured in 3068 subjects of the cohort aged at least 50 years. The respective Swiss cantonal ethical committees have granted ethical approval and participants gave written informed consent.

Arterial stiffness measurement

Mixed central and peripheral arterial stiffness was measured oscillometrically and simultaneously by CAVI and baPWV using a non-invasive VaSera VS-1500N vascular screening system (Fukuda Denshi, Tokyo, Japan). All measurements were taken in supine position after 10 min of rest in a quiet room with constant temperature. Blood cuffs were placed at each upper arm and above each ankle. ECG electrodes at each wrist and a phonocardiogram on the sternal border in the second intercostal space were applied to detect the initial notch of the pulse waves at the heart and the ankle on average over six heart cycles. The time delay of the pulse wave from the heart to the ankle was determined by a foot-to-foot-method. Vascular length between the heart valve and the ankle artery was estimated by the VSS-10 software (Fukuda Denshi) using a height based formula [24]. The PWV is calculated by dividing the arterial length by the time delay of the pulse wave. CAVI is then automatically derived from Bramwell-Hill's equation and the stiffness parameter β with an inclusion of the PWV [25]. Therefore, CAVI is less dependent on blood pressure at the time of measurement than aortic PWV [26] and baPWV [27]. The average of two consecutive measurements at 3–5 min intervals and of both body sides was taken for analyses. The CAVI and baPWV reproducibility was previously shown to be high in this Caucasian cohort [28]. CAVI reflects arterial stiffness of the aorta and the iliac, femoral and tibial arteries [25] and baPWV between the brachial and tibial arteries [29]. Since both of these indices cover different segments of the arterial tree, they reflect a combination of central and peripheral arterial stiffness [20, 21].

Physical activity assessment

The self-reported International Physical Activity Questionnaire (IPAQ) long version was administered to classify the PA level in 3072 individuals [30]. The IPAQ long form asks for the frequency and duration of moderate and vigorous PA in different domains performed during the last 7 days (leisure time PA, domestic and gardening (yard) activities, work-related PA, transport-related PA) [31]. Moderate and vigorous intensities were associated with harder and much harder breathing, respectively. Minutes per week of moderate PA (including walking), vigorous PA and total PA as a sum of minutes per week of moderate and vigorous PA were calculated following the IPAQ guidelines [31]. They were weighted by their energy cost as

metabolic equivalents (MET) with one MET equating to around one kcal/kg/hour, which approximately corresponds to sitting quietly. This leads to a MET-minutes per week score reflecting total energy expenditure [32]. Total PA is therefore a combined measure of amount and intensity of PA in terms of MET-minutes per week of moderate and vigorous PA. We calculated levels ("low", "medium" and "high") of each category of PA (moderate, vigorous and total PA). Levels of moderate and total PA were calculated by tertile classes. Vigorous PA was not categorized in tertiles due to the clustering of answers (56.8 % of subjects reported no vigorous PA and 6.2 % reported 960 MET-min/week of vigorous PA). All subjects without vigorous PA were assigned to the lowest level of vigorous PA (N = 1084). Since 118 subjects reported on exactly 960 MET-min/week of vigorous PA corresponding to the threshold between the medium and high level of vigorous PA, these subjects were all assigned to the medium level to achieve the best possible balance of group sizes. Thus, the chosen categorization of vigorous PA is the best approximation to a categorization by tertiles as for moderate and total PA.

Statistical analyses

If not stated otherwise, data are expressed as median (25th and 75th percentile). Comparisons of the variables of interest by PA levels were performed by using t test, nonparametric median test (Kruskal–Wallis test) or χ^2 test, as appropriate and age associations by linear regression. CAVI and baPWV were analyzed as continuous outcomes and when stated in dichotomized form, with a threshold for increased arterial stiffness of 9 for CAVI (comparing the highest to the lower two tertiles) and of 14.4 m/s for baPWV (comparing the highest to the lower two tertiles), respectively. We used univariable (Model 1) and multivariable mixed linear and logistic regression models for analyses including a random area effect to account for the multi-center study setting. In Model 2, the association of arterial stiffness with PA was adjusted for age and sex and in Model 3 additionally for body mass index, smoking status defined as packyears up to SAPALDIA 3, educational status, mean arterial pressure, heart rate, and medication. Medication intake was categorized in two classes: 0, no cardiovascular or metabolic disease related medication; 1, medication for kidney disease, diabetes, hyperlipidemia, hypertension, stroke, myocardial infarction, heart failure, angina and arrhythmia. We a priori defined and investigated several potentially important interactions and included the interaction terms age–sex and sex–mean arterial pressure in the final Model 4 based on the inclusion criteria $p = 0.1$. We used backward selection of variables using the Akaike Information Criterion (AIC) and tested non-linear terms using residual-versus-predicted-plots to derive the best fitting model. All statistical analyses were performed using the statistical software STATA (StataCorp LP, Release 12, Texas, USA) with $p = 0.05$ as significance level.

Results

Subject characteristics

In 1908 out of 3068 individuals data of both arterial stiffness and IPAQ were available. The analytic sample was on average significantly older (63.3 vs 58 years, $p < 0.001$) and had significantly lower baPWV (13.8 vs 14.1 m/s, $p < 0.001$), body mass index (26.1 vs 26.5 kg/m^2, $p < 0.05$), total PA (5279 vs 5810 MET-min/week, $p < 0.05$), vigorous PA (1023 vs 1454 MET-min/week, $p < 0.001$), mean arterial pressure (99.3 vs 100.3 mmHg, $p < 0.05$) and heart rate (61.9 vs 63.1 bpm, $p < 0.05$) compared to the whole arterial stiffness and IPAQ sample of SAPALDIA 3. CAVI, moderate PA and the number of smoking packyears were not significantly different. The main characteristics by vigorous PA levels are listed in Table 1.

Associations of age and sex with physical activity and arterial stiffness

A significant sex difference with respect to PA was present only in vigorous PA with higher values in males ($p < 0.001$) (Supplemental Table S1). There was a significant age associated decline in total PA for females ($p < 0.01$ oldest to youngest age category), but not for males ($p = 0.71$) (Supplemental Table S2). Vigorous PA decreased significantly in both sexes with increasing age category ($p < 0.001$ oldest to youngest age category). Moderate PA increased in both sexes from the age of 50-59 years to 60-69 years, significantly only in males ($p < 0.01$; females $p = 0.09$), and decreased in older participants with higher amounts of moderate PA compared to age 50–59 years significant only in males ($p = 0.03$), but not in females ($p = 0.53$). CAVI and baPWV increased significantly with age in both sexes (every $p < 0.001$); CAVI on average by 0.9 per decade and baPWV by 1.8 m/s, respectively (Supplemental Fig. S1). Statistically significant gender differences were observed for CAVI in the age groups 60–69 ($p < 0.001$) and 70–81 ($p < 0.01$) and for baPWV in the age groups 50–59 ($p = 0.01$) and 60–69 ($p < 0.01$), with lower values among women (Supplemental Fig. S1).

Table 1 Study population main characteristics across vigorous physical activity (PA) levels (N = 1898)

	Units	Vigorous PA level			*p*
		Low (N = 1084)	Medium (N = 326)	High (N = 488)	
Age	Years	65.0 (59.0; 70.9)	61.7 (55.8; 66.4)	60.9 (54.7; 66.3)	<0.001
baPWV	m/s	13.07 (12.27; 15.42)	13.00 (11.48; 14.60)	13.00 (11.48; 14.60)	<0.001
CAVI	No unit	8.72 (7.93; 9;47)	8.34 (7.64; 9.20)	8.40 (7.69; 9.05)	<0.001
Mean arterial pressure	mmHg	99 (92; 107)	98 (90; 105)	99 (92; 107)	0.37
Heart rate	bpm	62 (56; 69)	59 (54; 64)	60 (54; 65)	<0.001
Body mass index	kg/m^2	26.0 (23.3; 29.1)	25.3 (22.6; 27.5)	25.4 (23.0; 28.3)	0.01
Smoking	Packyears	0.4 (0; 20.0)	0 (0; 14.5)	2.0 (0; 20.0)	0.02
Moderate PA	MET-min/week	2832 (1356; 5292)	2753 (1449; 5202)	4821 (2588; 8148)	<0.001
Vigorous PA	MET-min/week	0 (0; 0)	680 (480; 960)	2880 (1860; 4580)	<0.001
Total PA	MET-min/week	2832 (1356; 5292)	3455 (2130; 6036)	8236 (5384; 11,909)	<0.001
		N (%)	N (%)	N (%)	*p*
Medication					
0		647 (34.1)	230 (12.1)	337 (17.8)	<0.001
1		437 (23.0)	96 (5.1)	151 (8.1)	
Medication for					
DKidney disease		3 (0.2)	3 (0.2)	0 (0)	
Diabetes		2 (0.1)	6 (0.3)	14 (0.7)	
Hyperlipidemia		190 (10.0)	42 (2.2)	62 (3.3)	
Hypertension		308 (16.2)	70 (3.7)	103 (5.4)	
Stroke		17 (0.9)	4 (0.2)	5 (0.3)	
Myocardial infarction		20 (1.1)	6 (0.3)	8 (0.4)	
Heart failure		8 (0.4)	2 (0.1)	4 (0.2)	
Angina pectoris		15 (0.8)	1 (0.1)	9 (0.5)	
Arrhythmia		40 (2.1)	8 (0.4)	10 (0.5)	
Education					
Low		64 (3.4)	10 (0.5)	18 (0.9)	0.15
Middle		700 (36.9)	213 (11.2)	328 (17.3)	
High		320 (16.9)	103 (5.4)	142 (7.5)	

BaPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; Education low, primary school; middle, secondary school, middle school or apprenticeship; high, Technical College or University; Medication 0, no cardiovascular or metabolic disease related medication; 1, medication for kidney disease, diabetes, hyperlipidemia, hypertension, stroke, myocardial infarction, heart failure, angina and arrhythmia; MET, metabolic equivalent; PA, physical activity. Values are median and 25th, 75th percentile or N (%). Percentages and *p* values for comparisons across vigorous PA levels. Percentages may not add up to 100 % due to rounding

Association of physical activity with arterial stiffness

In the univariable analyses the means of CAVI and baPWV both decreased across levels of moderate, vigorous and total PA, however significantly only for vigorous PA (every $p < 0.001$), where more than a third of the participants did not report on any vigorous PA. Tables 2 and 3 show the regression results for CAVI and baPWV as a function of PA for each of the four models. In the multivariable analyses of CAVI there was a significant inverse association of CAVI with PA after adjustment in Model 2 for total and vigorous PA comparing the high with the low PA level (each $p = 0.04$) and for moderate PA comparing the medium with the low PA level ($p = 0.03$), but not between high and low PA ($p = 0.09$). This inverse association was strengthened upon further adjustment in Model 3 with significant associations between the high and low PA level for total ($p = 0.03$) and vigorous PA ($p = 0.02$) and marginally significant for moderate PA comparing medium and low PA ($p = 0.05$), but not high and low PA ($p = 0.10$). Inclusion of the interaction terms age–sex and sex–mean arterial pressure in Model 4 further strengthened the associations of CAVI with the respective PA levels ($p = 0.02$–0.03). BaPWV showed negative and marginally significant associations with vigorous PA comparing the high with the low level and with moderate PA comparing the medium with the low level (each $p = 0.06$), but not significantly with total PA after adjustment in Model 3 and 4.

Table 2 Adjusted estimates of the association between physical activity (PA) levels and continuous cardio-ankle vascular index (CAVI)

	Unit	Model 1					Model 2				
		Coef.	95 % CI		*p*	AIC	Coef.	95 % CI		*p*	AIC
Moderate PA level		N = 1908				5766	N = 1896				4710
Medium versus low	MET-min/week	−0.05	−0.18	0.07	0.39		−0.10	−0.20	−0.01	0.03	
High versus low	MET-min/week	−0.03	−0.15	0.10	0.66		−0.08	−0.17	0.01	0.09	
Vigorous PA level		N = 1898				5694	N = 1886				4686
Medium versus low	MET-min/week	−0.29	−0.43	−0.16	<0.001		−0.06	−0.17	0.04	0.24	
High versus low	MET-min/week	−0.39	−0.50	−0.27	<0.001		−0.10	−0.19	0.01	0.04	
Total PA level		N = 1908				5763	N = 1896				4710
Medium versus low	MET-min/week	−0.06	−0.18	0.06	0.35		−0.08	−0.17	0.02	0.10	
High versus low	MET-min/week	−0.11	−0.24	0.01	0.07		−0.10	−0.19	−0.01	0.04	

	Unit	Model 3					Model 4					Adjusted (Model 4) CAVI mean
		Coef.	95 % CI		*p*	AIC	Coef.	95 % CI		*p*	AIC	
Moderate PA level		N = 1890				4620	N = 1890				4613	Low: 8.67
Medium versus low	MET-min/week	−0.09	−0.18	−0.00	0.05		−0.10	−0.19	−0.01	0.03		Medium: 8.57
High versus low	MET-min/week	−0.077	−0.17	0.01	0.10		−0.08	−0.18	0.01	0.08		High: 8.59
Vigorous PA level		N = 1880				4593	N = 1880				4588	Low: 8.64
Medium versus low	MET-min/week	−0.05	−0.16	0.05	0.32		−0.06	−0.16	0.04	0.26		Medium: 8.58
High versus low	MET-min/week	−0.11	−0.20	−0.02	0.02		−0.11	−0.20	−0.02	0.02		High: 8.53
Total PA level		N = 1890				4619	N = 1890				4613	Low: 8.67
Medium versus low	MET-min/week	−0.08	−0.17	0.01	0.09		−0.08	−0.17	0.01	0.08		Medium: 8.59
High versus low	MET-min/week	−0.10	−0.19	−0.01	0.03		−0.10	−0.20	−0.01	0.03		High: 8.56

AIC Akaike Information Criterion, *MET* metabolic equivalent

Model 1: univariable including a random area effect

Model 2: further adjusted for age, sex, body mass index, education and packyears of smoking

Model 3: further adjusted for mean arterial pressure, heart rate and medication

Model 4: further adjusted for interactions age–sex and sex–mean arterial pressure

Table 3 Adjusted estimates of the association between physical activity (PA) levels and continuous brachial-ankle pulse wave velocity (baPWV)

	Unit	Model 1					Model 2				
		Coef.	95 % CI		*p*	AIC	Coef.	95 % CI		*p*	AIC
Moderate PA level		N = 1907				8623	N = 1895				7722
Medium versus low	MET-min/week	−0.21	−0.48	0.05	0.11		−0.27	−0.48	−0.06	0.01	
High versus low	MET-min/week	−0.10	−0.36	0.16	0.45		−0.18	−0.38	0.03	0.09	
Vigorous PA level		N = 1897				8535	N = 1885				7688
Medium versus low	MET-min/week	−0.77	−1.05	−0.48	<0.001		−0.19	−0.43	0.04	0.11	
high versus low	MET-min/week	−0.81	−1.06	−0.56	<0.001		−0.15	−0.35	0.06	0.17	
Total PA level		N = 1907				8623	N = 1895				7725
Medium versus low	MET-min/week	−0.19	−0.45	0.07	0.16		−0.16	−0.37	0.05	0.13	
high versus low	MET-min/week	−0.21	−0.47	0.05	0.11		−0.15	−0.35	0.06	0.16	

	Unit	Model 3					Model 4					Adjusted (Model 4) PWV mean (m/s)
		Coef.	95 % CI		*p*	AIC	Coef.	95 % CI		*p*	AIC	
Moderate PA level		N = 1889				6968	N = 1889				6972	Low: 13.80
Medium versus low	MET-min/week	−0.16	−0.33	0.01	0.06		−0.16	−0.33	0.01	0.06		Medium: 13.63
High versus low	MET-min/week	−0.10	−0.27	0.07	0.24		−0.10	−0.27	0.07	0.25		High: 13.70
Vigorous PA level		N = 1879				6937	N = 1879				6940	Low: 13.77
Medium versus low	MET-min/week	−0.10	−0.29	0.10	0.33		−0.10	−0.29	0.10	0.31		Medium: 13.67
high versus low	MET-min/week	−0.17	−0.34	0.01	0.06		−0.16	−0.33	0.01	0.06		High: 13.60
Total PA level		N = 1889				6969	N = 1889				6973	Low: 13.78
Medium versus low	MET-min/week	−0.13	−0.30	0.04	0.13		−0.13	−0.30	0.04	0.13		Medium: 13.65
high versus low	MET-min/week	−0.10	−0.26	0.07	0.27		−0.10	−0.26	0.08	0.28		High: 13.69

AIC Akaike Information Criterion, *MET* metabolic equivalent

Model 1: univariable including a random area effect

Model 2: further adjusted for age, sex, body mass index, education and packyears of smoking

Model 3: further adjusted for mean arterial pressure, heart rate and medication

Model 4: further adjusted for interactions age–sex and sex–mean arterial pressure

There was a significant positive age–sex (each $p = 0.03$) and marginally significant positive sex–mean arterial pressure interaction (each $p = 0.05$) in the models estimating the association between CAVI and PA. With increasing mean arterial pressure, the sex difference in CAVI increased, with higher values in males for moderate, vigorous and total PA (exemplarily for total PA in Supplemental Fig. S2). The interaction terms were not statistically significant in the baPWV models.

The fully adjusted (Model 4) CAVI means decreased significantly from 8.67 to 8.56 from the high to the low total PA level, similarly from 8.64 to 8.53 for vigorous PA and from 8.67 for the low moderate PA level to 8.57 for the medium moderate PA level (Fig. 1). The fully adjusted baPWV means decreased non-significantly from 13.78 to 13.65 m/s across total PA levels (from low to medium), from 13.77 to 13.60 m/s for vigorous PA (from low to high) and from 13.80 to 13.63 m/s for moderate PA (from low to medium).

Odds ratios

The marginal probability of CAVI ≥ 9 decreased from 0.37 to 0.31 ($p < 0.01$) significantly across vigorous PA levels with an odds ratio (OR) of 0.65 (95 % Confidence Interval (CI) 0.48–0.88) for the highest level compared to the lowest, and marginally significant from 0.37 to 0.33 across total PA levels ($p = 0.07$, OR 0.76, 95 % CI 0.57–1.02), and from 0.38 to 0.34 across moderate PA levels ($p = 0.06$, OR 0.75, 95 % CI 0.56–1.01). These results are derived from mixed logistic regression analyses with the same adjustment as in Model 4 (Table 4 and Supplemental Fig. S3). Similarly, the marginal probability of baPWV ≥ 14.4 decreased significantly from 0.33 to 0.28 for vigorous PA levels ($p = 0.02$, OR 0.67, 95 % CI 0.48–0.93), but non-significantly across the total (from 0.33 to 0.32, $p = 0.53$, OR 0.91, 95 % CI 0.66–1.23) and moderate PA levels (from 0.33 to 0.32, $p = 0.69$, OR 0.94, 95 % CI 0.69–1.28).

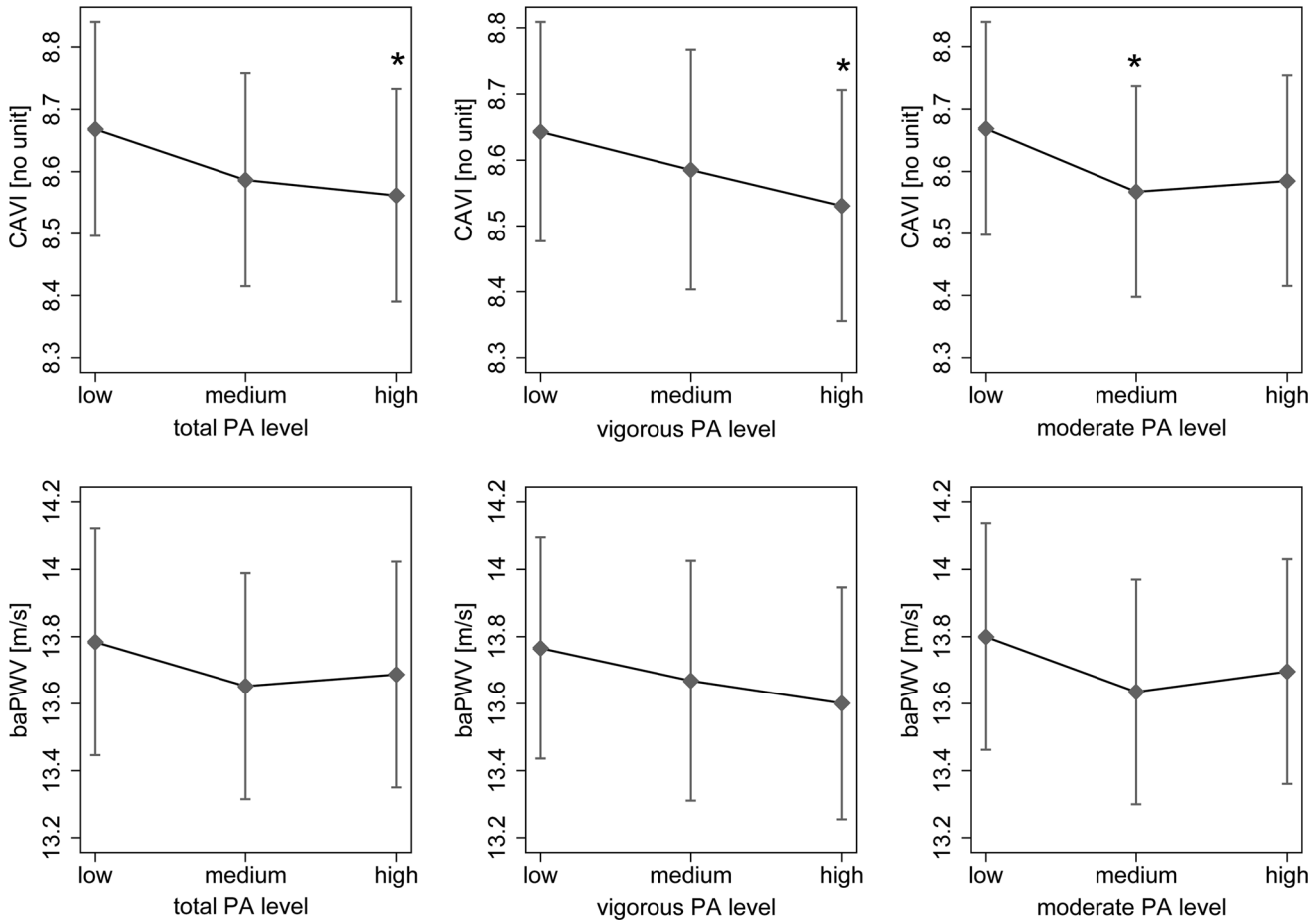

Fig. 1 Fully adjusted (Model 4) means of cardio-ankle-vascular-index (CAVI) and brachial-ankle pulse wave velocity (baPWV) across total, vigorous and moderate physical activity (PA) levels. *$p < 0.05$ compared to low PA level

Table 4 Odds ratios (OR) of cardio-ankle vascular index (CAVI) ≥ 9 and brachial-ankle pulse wave velocity (baPWV) ≥ 14.4 m/s across moderate, vigorous and total physical activity (PA)

Variable	PA	Medium compared to low PA level				High compared to low PA level			
		OR	95 % CI		*p*	OR	95 % CI		*p*
CAVI	Total	0.87	0.65	1.17	0.36	0.76	0.57	1.02	0.07
	Vigorous	0.91	0.65	1.27	0.60	0.65	0.48	0.88	<0.01
	Moderate	0.75	0.56	1.01	0.06	0.75	0.56	1.01	0.06
baPWV	Total	0.94	0.68	1.29	0.69	0.91	0.66	1.24	0.53
	Vigorous	0.93	0.64	1.34	0.69	0.67	0.48	0.93	0.02
	Moderate	0.89	0.64	1.22	0.46	0.94	0.69	1.28	0.69

Discussion

The results of this cross-sectional study in a very well characterized cohort of elderly Caucasian subjects from the general population suggest that higher levels of self-reported PA are associated with lower arterial stiffness, even after adjustment for several potential confounders. Especially vigorous PA was linked with lower arterial stiffness in this ageing population. These data support the importance of PA for improving cardiovascular health in elderly people and suggest that vigorous PA promotion in this age group may prevent against increased arterial stiffness resulting from atherosclerotic processes.

Our results are in agreement with previous cross-sectional studies which suggest that higher levels of PA may have a protective effect on the vascular system [16, 17]. Thereby, it has to be kept in mind, that the effect of PA on arterial stiffness varies across the arterial tree [15, 33]. In a comparable cohort of older adults of the Whitehall II study higher arterial stiffness measured as carotid-femoral PWV was strongly associated with reduced walking speed and self-reported physical functioning [16]. Similarly, lower walking speed was linked with increased carotid-femoral PWV in a general population aged 70–79 years of the Health ABC Study, however, this association was dependent on the presence of hypertension and other vascular risk factors [17]. Aoyagi et al. [33] examined the association of habitual PA (>3 metabolic equivalents) measured by step counts and arterial stiffness in 198 Japanese people aged 65–84 years . They reported on a beneficial effect of PA on the stiffening of central arteries, but not on the peripheral vasculature. Controversial results can be found regarding the intensity-dependence of this PA effect. In a medium sized longitudinal study particularly PA at higher intensity was favorable regarding central and peripheral arterial stiffness in younger persons [14, 15]. In the only study analyzing baPWV and PA intensities an increase in moderate-to-vigorous PA, but not light intensity PA, was linked with a decrease of baPWV in 274 overweight and obese young adults longitudinally within 1 year [20]. In 103 postmenopausal women moderate and vigorous PA was inversely associated with central arterial stiffness [19]. Yet, also long-term maintenance of low intensity PA was associated with lower central arterial stiffness in older adults [18].

Intervention studies with rather small sample sizes have demonstrated that arterial stiffness may be modifiable by exercise training in older adults [34–36]. A 1 year vigorous endurance exercise program improved arterial stiffness indices in twelve persons aged on average 70.3 years, who were sedentary before [34]. However, a short-term 12 week moderate intensity PA program did not change arterial stiffness in 113 persons aged 50–80 [37]. Five recent systematic reviews of intervention studies show conflicting results concerning the effects of exercise interventions on arterial stiffness. Two of them found a significant positive effect of aerobic exercise on arterial stiffness especially at higher intensity [35, 36], however neither in pre- and hypertensive [38] nor in middle-aged and older obese persons [39]. The results regarding resistance training are controversial ranging from negative effects [40] to beneficial effects depending on the intensity, muscle groups involved and the movement execution [35, 36]. The discrepancies in these results may be due to whether or not non-randomized controlled trials have been included in the reviews, small sample sizes for subgroup analyses, different arterial stiffness measures, and varying statistical analyses. Thus, intervention study results show that there are beneficial effects of exercise training on arterial stiffness depending on the intensity and modality [34–37]. Our results show an association in line with these intervention study effects in terms of a beneficial relationship between higher amounts of regularly performed PA, especially at higher intensity, on arterial stiffness in older adults at the population level.

CAVI and baPWV are valid vascular biomarkers for non-invasive arterial stiffness assessment and are associated with cardiovascular disease risk and outcomes [41–44]. Both CAVI and baPWV have shown good correlations with central arterial stiffness [29, 45]. In a systematic review of clinical studies, a 1 m/s reduction in baPWV was associated with an increase in total cardiovascular events, cardiovascular mortality, and all-cause mortality by 12, 13, and 6 %, respectively [43]. CAVI is methodologically

based on the baPWV measurement with improvements regarding the correlation with blood pressure [25]. Since CAVI is mathematically derived from the stiffness parameter β and a modified Bramwell-Hill equation, CAVI could be shown to be less dependent on the blood pressure at the time of measurement compared to baPWV [27]. CAVI includes stiffness of the aorta, femoral artery and tibial artery [25], whereas baPWV reflects the PWV to the upper arm and foot ignoring the influence of PWV to the arm as a possible modifier of the overall stiffness without precise definition of the distance from the heart to the upper arm [46]. These differences between CAVI and baPWV might explain that both indices do not show exactly the same results concerning their association with PA. However, they point to consistent conclusions towards lower arterial stiffness with higher PA.

CAVI and baPWV were on average 0.10 and 0.16 m/s, respectively, lower in persons of the high PA level compared to the low PA level across moderate, vigorous and total PA in the fully adjusted Model 4. Thereby, it has to be kept in mind that moderate and total PA levels have been generated according to tertiles of MET-min/week, while this was not possible for vigorous PA where more than a third of subjects (N = 1084) did not report on any vigorous. In this general population aged 50–81 years, CAVI increased significantly on average by 0.87 per decade and baPWV by 1.84 m/s (see Supplemental Fig. S1). Therefore, higher levels of PA were associated with a favorable decrease of CAVI corresponding to around 1.1 years and for baPWV to 0.9 years of age related decrease in arterial stiffness independent of the main confounding factors. This strengthens the evidence that PA can be implemented in cardiovascular health guidelines to counteract the vascular aging process and prevent early vascular aging as suggested by Nilsson et al. [9]. Nevertheless, due to the cross-sectional design of this study causality and reverse causality concerning PA and arterial stiffness cannot be answered. Up-to-date there are no studies on sedentary behavior and systemic arterial stiffness, however sitting time has been shown to be related to higher wave reflections [47], augmentation index [48] and carotid arterial stiffness [49].

Presently, there are no comparable IPAQ data for a Swiss population based cohort. According to the Eurobarometer 64.3 our study sample of the Swiss general population of older adults would rank as one of the most active European nations (median total PA 3971 MET-minutes/week) [50]. This is in line with reports that 73 % of Swiss adults meet the current PA guidelines according to the recent Swiss health survey [51] and is consistent with the 2014 Swiss report on sports activity, in which Switzerland ranks 2nd behind Sweden in a European comparison [52, 53]. However, only 43 % of our ageing population reported on vigorous PA. This part of the population showed a beneficial inverse association of vigorous PA with arterial stiffness compared to subjects without vigorous PA. This result indicates that population based PA interventions and guidelines for older adults should incorporate and promote vigorous PA to improve cardiovascular health.

Self-reported medication is commonly used for assessing disease in epidemiological studies and is related to diagnosed disease as shown for diabetes [54]. Assessment of disease by self-report of medication may be prone to information bias due to non-reporting leading to misclassification. However, it can be assumed that this would be nondifferential misclassification without affecting the estimates in this cohort study [55]. Besides, medical treatment is commonly based on clear disease indications and it has been shown, that self-reported medical history is accurately related to cardiovascular and metabolic disease [56, 57]. Furthermore, patients' self-reported cardiovascular and diabetic medication use has been found to be reliable [58].

Study limitations

This is a cross-sectional study, which does not enable inferring a causal association between PA and arterial stiffness in these adults aged at least 50 years. Reporting bias might have affected the self-reported PA assessment. However, the IPAQ has been developed and validated by Craig et al. [30] as a cross-national monitoring tool of PA and physical inactivity for adults aged 15–69 years and represents a feasible, reliable and valid measurement instrument of PA. While the IPAQ is prone to over-estimating PA especially in adults aged ≥65 years [59], this is less the case for vigorous PAs such as structured sports or exercise activities [60], which showed the strongest association with arterial stiffness in our study. Due to logistic and financial reasons, objective PA measurements could not be implemented in the current study.

Conclusions

In summary, PA of higher intensity was independently associated with lower mixed central and peripheral arterial stiffness in this cross-sectional analysis of a cohort of older adults. The probability of having increased arterial stiffness was lower in more physically active persons. Regular vigorous PA may counteract vascular aging and, thus, reduce the population risk of cardiovascular disease and events. It is highly recommended to further strengthen the significance of vigorous PA in cardiovascular health guidelines in these age groups.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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Supplemental figures

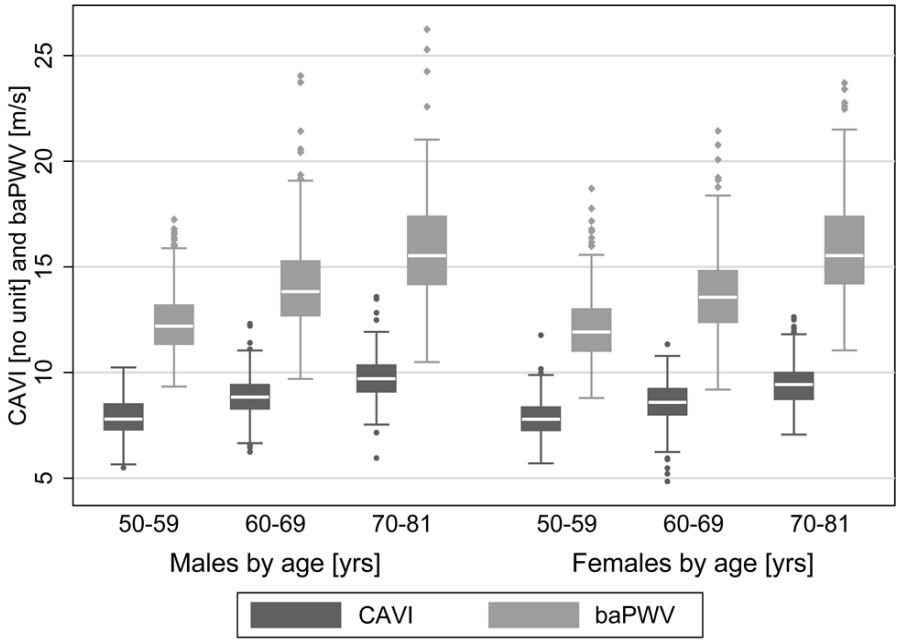

Fig. S1 Box plots of cardio-ankle-vascular-index (CAVI) and brachial-ankle pulse wave velocity (baPWV) by sex and age. Box represents 25th percentile (lower edge), median (middle bar) and 75th percentile (upper edge). Whiskers show the extent of the rest of the data; points indicate outliers.

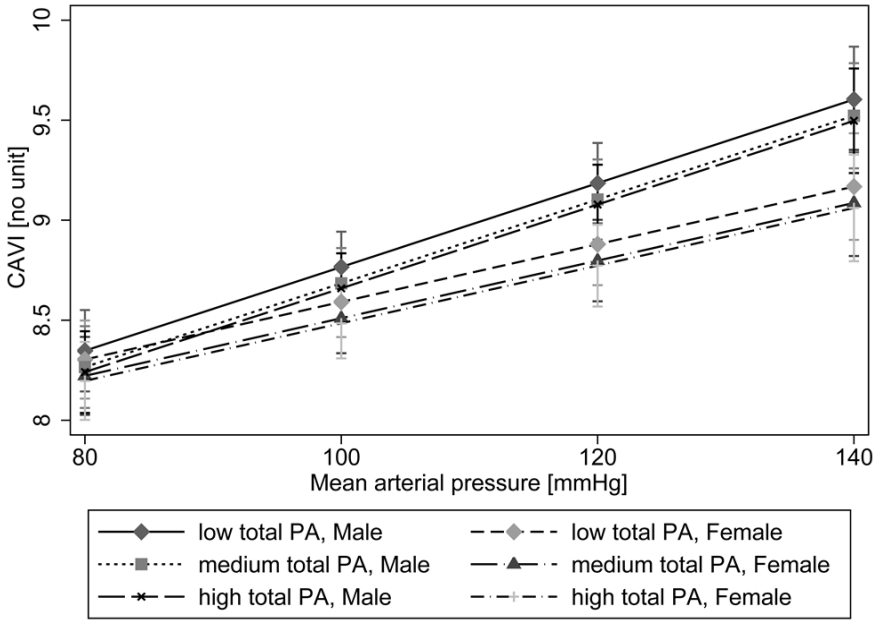

Fig. S2 Fully adjusted (Model 4) means of cardio-ankle-vascular-index (CAVI) over mean arterial pressure by sex and total physical activity (PA) levels (low, medium, high).

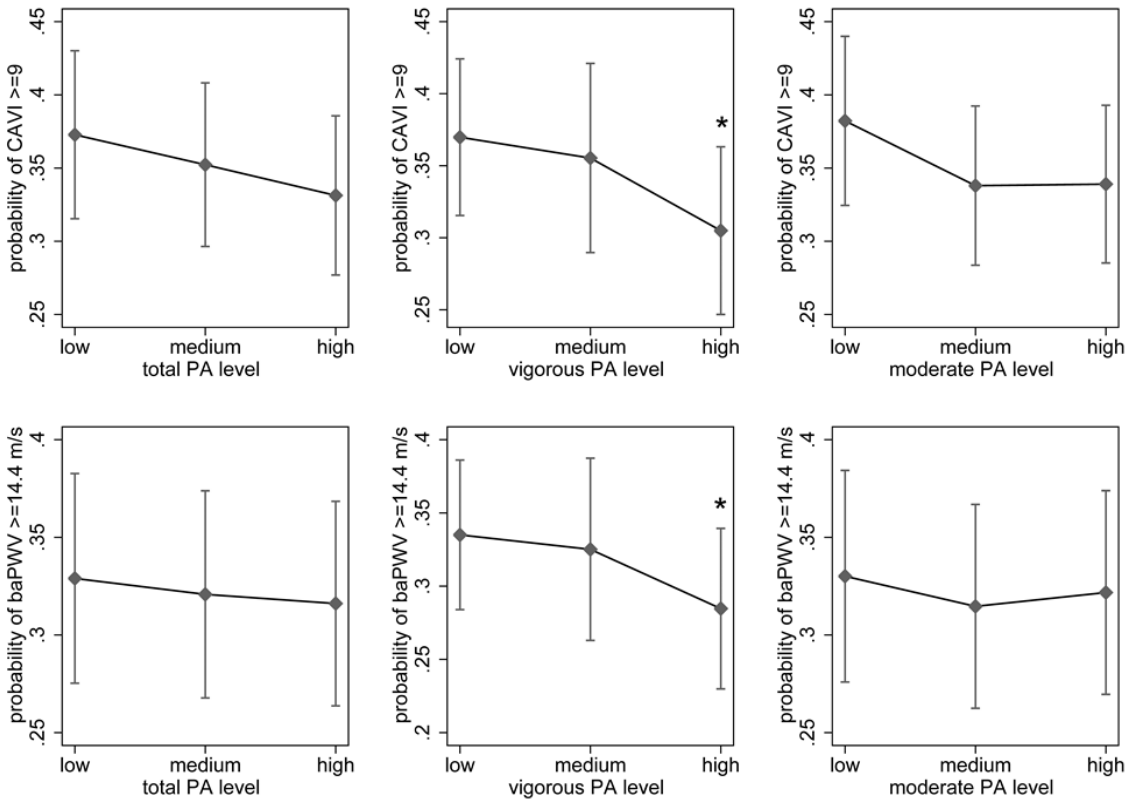

Fig. S3 Marginal probability of cardio-ankle vascular index (CAVI) >=9 and brachial-ankle pulse wave velocity (baPWV) >=14.4 m/s across total, vigorous and moderate physical activity (PA) levels. * $p < 0.05$ compared to low PA level.

Supplemental tables

Supplemental Table S1. Study population main characteristics by sex.

	Units	N	Male (N=923)	Female (N=985)	P-value
Age	Years	1908	63.9 (57.7; 69.0)	62.6 (56.3; 68.8)	0.17
baPWV	m/s	1907	13.55 (12.19; 15.27)	13.24 (11.89; 14.84)	<0.05
CAVI	no unit	1908	8.74 (7.88; 9;44)	8.46 (7.75; 9.20)	<0.001
Mean arterial pressure	mmHg	1906	100 (93; 108)	97 (90; 105)	<0.001
Heart rate	Bpm	1904	61 (55; 67)	61 (56; 67)	0.38
Body mass index	kg/m2	1908	26.6 (24.4; 29.3)	24.5 (21.9; 27.8)	<0.001
Smoking	packyears	1896	4 (0; 24)	0 (0; 12)	<0.001
Medication		1908	N (%)	N (%)	<0.001
0			533 (57.7)	699 (71.0)	
1			292 (31.6)	241 (24.5)	
2			98 (10.6)	45 (4.6)	
Education		1908	N (%)	N (%)	<0.001
Low			27 (2.9)	66 (6.7)	
Middle			538 (58.3)	712 (72.3)	
High			358 (38.8)	207 (21.0)	
Moderate PA	MET-min/week	1908	3066 (1634; 5978)	3447 (1688; 6095)	0.32
Low	N (%)		296 (32.1)	294 (29.8)	
Medium	N (%)		317 (34.3)	338 (34.3)	
High	N (%)		310 (33.6)	353 (35.8)	
Vigorous PA	MET-min/week	1898	0 (0; 1680)	0 (0; 960)	<0.001
Low	N (%)		466 (50.7)	618 (63.1)	
Medium	N (%)		168 (18.3)	158 (16.1)	
High	N (%)		285 (31.0)	203 (20.7)	
Total PA	MET-min/week	1908	3948 (2066; 7818)	3975 (1968; 6997)	0.32
Low	N (%)		301 (32.6)	316 (32.1)	
Medium	N (%)		289 (31.3)	346 (35.1)	
High	N (%)		333 (36.1)	323 (32.8)	

BaPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; Education low, primary school; middle, secondary school, middle school or apprenticeship; high, Technical College or University; Medication 0, no medication intake, 1, hyperlipidemia, kidney disease, hypertension, arrhythmia medication, 2, diabetes, myocardial infarction, heart insufficiency, stroke medication; MET, metabolic equivalent; PA, physical activity. Values are median and 25^{th}, 75^{th} percentile or N (%).

Supplemental Table S2. Moderate, vigorous and total physical activity (PA) by age and sex.

	Unit	Male (N=923)			P-value	Female (N=985)			P-value
		50-59 years	60-69 years	70-81 years		50-59 years	60-69 years	70-81 years	
Moderate PA	MET-min/week	2643 (1200; 5362)	3436 (1881; 6059)	3199 (1645; 6582)	0.03	3294 (1778; 5784)	3603 (1830; 6264)	3449 (1215; 5814)	0.53
Vigorous PA	MET-min/week	720 (0; 1920)	0 (0; 1800)	0 (0; 840)	<0.001	0 (0; 1440)	0 (0; 720)	0 (0; 0)	<0.001
Total PA	MET-min/week	3666 (1728; 7818)	4442 (2330; 7947)	3946 (1853; 7629)	0.71	4158 (2136; 7636)	4080 (2160; 7050)	3642 (1245; 6204)	<0.01

MET, metabolic equivalent; PA, physical activity. Values are median and 25th, 75th percentile.

Supplemental Material 5: SAPALDIA Acknowledgement

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Chapter 6

Publication 3: Long-term Physical Activity & Arterial Stiffness

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Long-term physical activity is associated with reduced arterial stiffness in older adults: longitudinal results of the SAPALDIA cohort study

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Abstract

Background: longitudinal analyses of physical activity (PA) and arterial stiffness in populations of older adults are scarce. We examined associations between long-term change of PA and arterial stiffness in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).
Methods: we assessed PA in SAPALDIA 2 (2001–03) and SAPALDIA 3 (2010–11) using a short questionnaire with a cut-off of at least 150 min of moderate-to-vigorous PA per week for sufficient activity. Arterial stiffness was measured oscillometrically by means of the brachial-ankle pulse wave velocity (baPWV) in SAPALDIA 3. We used multivariable mixed linear regression models adjusted for several potential confounders in 2,605 persons aged 50–81.
Results: adjusted means of baPWV were significantly lower in persons with sufficient moderate-to-vigorous PA (i) in SAPALDIA 2 but not in SAPALDIA 3 ($P = 0.048$) and (ii) in both surveys ($P = 0.001$) compared with persons with insufficient activity in both surveys. There was a significant interaction between sex and the level of change in PA concerning baPWV ($P = 0.03$). The triples of parameter estimates describing the association between level of PA change and baPWV were not significantly different between the two sex-specific models ($P = 0.07$).
Conclusions: keeping up or adopting a physically active lifestyle was associated with lower arterial stiffness in older adults after a follow-up of almost a decade. Increasing the proportion of older adults adhering to PA recommendations incorporating also vigorous PA may have a considerable impact on vascular health at older age and may contribute to healthy ageing in general.

Keywords: *arterial stiffness, cardiovascular disease, longitudinal, physical activity, pulse wave velocity, older people*

Introduction

Early vascular ageing is a major determinant of increased cardiovascular (CV) risk [1]. Structural changes of the arterial system related to advanced ageing such as accelerated thickening of the arterial wall, degeneration of elastin and collagen proliferation are associated with higher arterial stiffness [2]. The velocity of the pulse waves propagating along the arterial wall is a measure of stiffening of the vasculature and increased CV risk [3]. Increased arterial stiffness was found to be independently associated with increased CV risk and CV events, as well as all-cause and CV mortality [4, 5]. Furthermore, arterial stiffness is an important surrogate end point of CV disease, because it reflects not only target organ damage but also

pathological processes and underlying risk factors connected with vascular ageing [3, 5].

Lack of physical activity (PA) is a well-documented risk factor for CV disease [6, 7] and one of the main components of the global burden of disease [8]. PA has been shown to be a modifiable lifestyle factor with the potential to decelerate vascular ageing and arterial stiffness in short-term interventional studies up to 16 weeks including persons aged 18–72 [9]. A physically active lifestyle throughout life has protective effects on the vasculature and the risk of CV events also in older adults with accelerated vascular modifications [10]. In cross-sectional population-based studies of older adults, PA at both light and moderate-to-vigorous intensity was beneficially associated with lower arterial stiffness compared with inactive persons [11–13].

There are no longitudinal population-based studies of PA and arterial stiffness measured as brachial-ankle pulse wave velocity (baPWV) in older adults. baPWV is correlated with higher risk of CV events and all-cause mortality [14]. In 274 overweight young adults, a 1-year increase in moderate PA was associated with lower baPWV, suggesting a reduction of future CV risk [15]. On the basis of this lack of longitudinal evidence in ageing populations, the present study aimed at examining the associations of long-term PA and change of PA with arterial stiffness in a cohort of community-dwelling adults aged 50–81. The main question was whether even older adults benefit from adopting a physically active lifestyle in terms of lower arterial stiffness and CV risk in the long term.

Methods

Study design and participants

The Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) is an ongoing multicentre cohort study initiated in 1991 among randomly selected adults (18–65 years, $n = 9{,}651$) [16]. The present analyses include all participants who gave information on their PA behaviour in SAPALDIA 2 (year 2001–03) and SAPALDIA 3 (year 2010–11) and participated in the arterial stiffness measurements in SAPALDIA 3 ($n = 2{,}605$). Participants gave written informed consent, and the respective Swiss cantonal ethical committees had granted ethical approval.

Arterial stiffness measurement

Arterial stiffness was measured oscillometrically in SAPALDIA 3 by the baPWV using a VaSera VS-1500N vascular screening system (Fukuda Denshi, Tokyo, Japan). The reproducibility of this measurement has been shown to be high with a mean coefficient of variation of 3.9% in the studied population [17]. All measurements were performed in a quiet room with constant temperature in supine position after 10 min of rest. A detailed description of this measurement has been reported previously [17]. In brief, blood cuffs were placed at each upper arm and above each ankle. ECG electrodes at each wrist and a phonocardiogram on the sternal border in the second intercostal space were attached. PWV was calculated automatically by the VSS-10 software (Fukuda Denshi) by dividing the arterial length between the sites of interest on the basis of a height-based formula by the time delay of the pulse wave determined by a foot-to-foot method.

Physical activity assessment

The same short self-reported PA questionnaire was administered to classify the participants' PA level in SAPALDIA 2 and SAPALDIA 3 [18]. Four questions were asked regarding the frequency and duration of PA per week. PA associated with getting a bit out of breath was categorised as moderate intensity PA and with getting out of breath and sweating as vigorous intensity PA. We calculated minutes per week of moderate and vigorous PA and summed these two to moderate-to-vigorous PA, whereby minutes derived from vigorous PA were counted twice [19]. Participants with at least 150 min/week of moderate-to-vigorous PA or at least 1 h of vigorous PA were categorised as active, both in SAPALDIA 2 and in SAPALDIA 3, and participants with less as inactive [19]. The participant's change of PA from SAPALDIA 2 to SAPALDIA 3 was categorised as follows: (i) as remaining inactive if the participant was inactive in both assessments, (ii) as becoming inactive if active in SAPALDIA 2 but inactive in SAPALDIA 3, (iii) as becoming active if inactive in SAPALDIA 2 but active in SAPALDIA 3 and (iv) as remaining active if active in SAPALDIA 2 and 3.

Co-variates

Age at the time of the SAPALDIA 3 baPWV assessment and sex were taken as primary co-variates. Change of body mass index (BMI [kg/m^2]) was calculated as BMI of SAPALDIA 3 minus BMI of SAPALDIA 2. Heart rate, diastolic and systolic blood pressure were measured in sitting position after 10 min of rest in SAPALDIA 2 and 3 (Omron 705IT, Omron Healthcare, Japan). Mean arterial pressure was calculated as mean arterial pressure = [(2 × diastolic blood pressure) + systolic blood pressure]/3. Medication was assessed by a self-administered questionnaire in SAPALDIA 3 and coded as 0, for no medication intake; 1, for hyperlipidaemia, kidney disease and hypertensive medication; 2, for diabetes, arrhythmia, myocardial infarction, heart failure and stroke medication. Socioeconomic status was assessed by the maximal level of education in SAPALDIA 2 and 3 (low: primary school; middle: secondary school, middle school or apprenticeship; high: Technical College or University). Pack-years of cigarettes smoked were calculated in SAPALDIA 2 and 3.

Statistical analyses

Unless stated otherwise, data are expressed as mean (standard deviation [SD]). Sex differences in the variables were assessed using *t*-tests or non-parametric Wilcoxon–Mann–Whitney tests as appropriate. We analysed the association between long-term change in PA from SAPALDIA 2 to SAPALDIA 3 and arterial stiffness in SAPALDIA 3 using multivariable mixed linear regression models. Based on the literature and previous

analyses in this cohort, we pre-selected potential confounding co-variates. Co-variates were considered as potential confounders if the *P*-value of their association with the respective outcome was <0.2. We used backward selection of variables using the Akaike Information Criterion (AIC) and tested non-linear terms to derive the best fitting model. We tested a set of interaction terms between PA, age, sex and mean arterial pressure to be included in the final model if $P < 0.1$. The fully adjusted model included age, sex, mean arterial pressure, heart rate, change of BMI, pack-years of cigarettes smoked, educational level, medication intake and an interaction term between change of PA and sex as fixed effects, and study area as random effect to account for the multi-centre study setting. Chi-square tests were used to compare effect estimates of sex-stratified analyses. All statistical analyses were performed using the statistical software STATA (StataCorp LP, USA) with $P < 0.05$ defining statistical significance.

Results

The mean follow-up time was 8.3 (SD 0.5) years. The final analytic sample consisted of 2,605 participants with complete data. In SAPALDIA 3, the cohort was on average 63.4 (SD 8.0) years old with 50.7% of them being females, mean BMI 26.3 (SD 4.3) kg/m^2, had a mean arterial pressure of 99.7 (SD 11.5) mmHg and a mean baPWV of 13.8 (SD 2.5) m/s. Among them, 74.0% were sufficiently active with at least 150 min of moderate-to-vigorous PA in SAPALDIA 2 and 75.1% in SAPALDIA 3. The main characteristics by sex and PA level for SAPALDIA 2 and 3 are listed in Tables 1 and 2.

The mean of minutes per week of moderate PA was significantly higher by 23.9% in SAPALDIA 3 than in SAPALDIA 2 (median 180 [inter-quartile range 60, 360] versus 180 (60, 420) min/week, $P < 0.001$). Vigorous PA decreased significantly in all participants on average by 18% from SAPALDIA 2 to 3 (median 30 [inter-quartile range 0, 150] versus 30 (0, 60) min/week, $P < 0.001$). BMI (mean 25.7 [SD 4.0] versus 26.3 [SD 4.3] kg/m^2) and mean arterial pressure (mean 96.2 (SD 12.9) versus 98.1 (SD 12.1) mmHg (each $P < 0.001$) increased significantly in both sexes from SAPALDIA 2 to 3. Mean heart rate decreased from 70.0 (SD 10.2) to 69.2 (SD 10.3) bpm ($P < 0.001$).

baPWV was lower in persons with sufficient PA in one of the two or both SAPALDIA follow-ups compared with persons with insufficient PA in both assessments. In the entire cohort, covariate-adjusted means of baPWV were significantly lower in persons with sufficient moderate-to-vigorous PA (i) in SAPALDIA 2 but not in SAPALDIA 3 ($P = 0.048$) and (ii) in both surveys ($P = 0.001$) compared with persons with insufficient activity in both surveys (Figure 1).

There was a significant interaction between sex and the level of change in PA concerning baPWV ($P = 0.03$). The fully covariate-adjusted means of baPWV were significantly lower in men becoming active (13.8 m/s, $P = 0.04$) and in men remaining active (13.8 m/s, $P = 0.01$) compared with men remaining inactive (14.3 m/s). In females with sufficient activity in SAPALDIA 2 but not in SAPALDIA 3 (13.6 m/s, $P = 0.02$) and in females remaining active (13.7 m/s, $P = 0.03$), the fully covariate-adjusted means of baPWV were significantly lower compared with females remaining inactive (13.9 m/s). Analyses stratified by sex confirmed these results. The triples of parameter estimates describing the association between level of PA change and baPWV were not significantly different between the two sex-specific models ($P = 0.07$).

Discussion

Key findings

In this longitudinal cohort study of older adults, adoption or maintenance of a physically active lifestyle over an average time of 8.3 years was associated with lower arterial stiffness in males and in females later in life. As our analyses were adjusted for several potential confounders, this is suggestive of an independent association. In the total study population, individuals with insufficient PA in both surveys had higher CV risk in terms of higher arterial stiffness compared with persons with sufficient PA in at least one of the two surveys.

Previous cross-sectional studies of adults aged 60 years and older have shown that a higher amount of regular PA of light and moderate-to-vigorous intensity was associated with lower aortic stiffness measured as carotid-femoral pulse wave

Table 1. Main characteristics by sex and moderate-to-vigorous physical activity (PA) level in SAPALDIA 2

	Units	Female (n = 1,316)		*P* value	Male (n = 1,289)		*P* value
		Inactive	Active		Inactive	Active	
n (%)		377 (28.6)	939 (71.4)		299 (23.2)	990 (76.8)	
Age	Mean (SD) years	54.7 (7.7)	55.5 (8.2)	0.10	55.4 (7.7)	55.0 (8.0)	0.49
BMI	Mean (SD) kg/m^2	25.3 (4.4)	24.7 (4.2)	<0.05	27.0 (3.3)	26.4 (3.4)	<0.05
MAP	Mean (SD) mmHg	92.4 (11.8)	92.3 (12.5)	0.85	100.8 (11.8)	99.8 (12.5)	0.20
Heart rate	Mean (SD) bpm	71.1 (9.5)	70.2 (9.6)	0.12	71.3 (10.2)	68.8 (10.8)	<0.001
Smoking	Median (p25, p75) pack-years	1 (0, 18)	0.4 (0, 17)	0.65	3.8 (0, 21)	0 (0, 16)	0.005
Education	*n* (%)						
Low		39 (9)	55 (6)	0.30	20 (5)	22 (2)	
Middle		307 (71)	651 (74)		221 (60)	534 (58)	
High		85 (20)	179 (20)		126 (35)	366 (40)	<0.05
Moderate PA	Median (p25, p75) min/week	15 (0, 60)	240 (120, 420)	<0.001	5 (0, 60)	225 (120, 420)	<0.001
Vigorous PA	Median (p25, p75) min/week	0 (0, 0)	60 (0, 150)	<0.001	0 (0, 0)	60 (30, 150)	<0.001

BMI, body mass index; MAP, mean arterial pressure; p25, 25th percentile; p75, 75th percentile. *P* values relate to sex-specific differences between active and inactive persons.

Table 2. Main characteristics by sex and moderate-to-vigorous physical activity (PA) level in SAPALDIA 3

	Units	Female (n = 1,316)		P value	Male (n = 1,289)		P value
		Inactive	Active		Inactive	Active	
n (%)		371 (28.2)	945 (71.8)		277 (21.5)	1,012 (78.5)	
Age	Mean (SD) years	63.8 (8.5)	63.5 (7.8)	0.59	62.8 (8.4)	63.7 (7.7)	0.08
BMI	Mean (SD) kg/m^2	26.0 (4.9)	25.2 (4.5)	<0.05	27.6 (4.0)	27.0 (3.6)	<0.05
baPWV	Mean (SD) m/s	13.8 (2.6)	13.7 (2.4)	0.56	14.2 (2.6)	13.9 (2.4)	0.11
MAP	Mean (SD) mmHg	95.7 (12.3)	96.2 (12)	0.45	100.3 (11.4)	100.3 (11.9)	0.93
Heart rate	Mean (SD) bpm	70.5 (10.1)	69.0 (9.3)	<0.05	70.9 (10.4)	68.2 (11.2)	<0.001
Smoking	Median (p25, p75) pack-years	0.2 (0, 16.8)	0 (0, 11)	<0.05	3.8 (0, 30.5)	5 (0, 26)	0.73
Medication	n (%)						
0		259 (64)	655 (72)	<0.05	168 (51)	561 (58)	
1		113 (28)	204 (22)		115 (35)	275 (29)	
2		31 (8)	54 (6)		45 (14)	125 (13)	<0.05
Education	n (%)						
Low		46 (11)	48 (5)	<0.05	16 (5)	26 (3)	
Middle		281 (70)	677 (74)		189 (58)	566 (59)	
High		76 (19)	188 (21)		123 (37)	369 (38)	<0.05
Moderate PA	Median (p25, p75) min/week	0 (0, 60)	270 (180, 420)	<0.001	0 (0, 60)	300 (180, 540)	<0.001
Vigorous PA	Median (p25, p75) min/week	0 (0, 0)	60 (0, 150)	<0.001	0 (0, 0)	60 (30, 150)	<0.001

BMI, body mass index; MAP, mean arterial pressure; Medication 0, for no medication intake; 1, for hyperlipidaemia, kidney disease, hypertension and arrhythmia medication; 2, for diabetes, myocardial infarction, heart failure and stroke medication. p25, 25th percentile; p75, 75th percentile. P values relate to sex-specific differences between active and inactive persons.

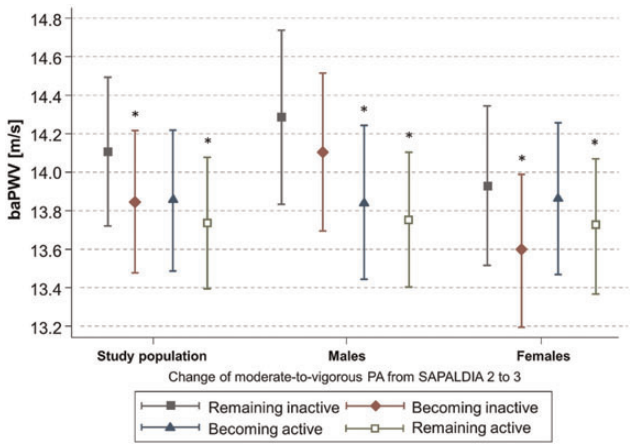

Figure 1. Fully co-variate-adjusted means of baPWV across different levels of change in moderate-to-vigorous physical activity (PA) from SAPALDIA 2 to 3, by sex. Underlying models included age, change of body mass index, mean arterial pressure, heart rate, education, medication, pack-years of cigarettes smoked and an interaction term between sex and change of PA as fixed effects and study area as random effect. *Statistically significant compared with remaining inactive.

velocity [11, 12]. In addition, physical functioning in terms of walking speed was inversely related to aortic stiffness in older adults of the Whitehall II Study in a cross-sectional analysis [20]. The American Heart Association defined regular PA of at least 150 min of at least moderate intensity PA per week as one component of a so-called ideal CV health behaviour [21]. In a 4- to 5-year follow-up among 505 Caucasian persons with a mean age of 61.6 years, adherence to a lifestyle complying with all of the components of an ideal CV health was associated with significantly lower carotid-femoral pulse wave velocity compared with persons with a maximum of two of these CV health components [22]. The independent contribution of long-term PA and change of PA apart from other health behaviours was not assessed in this study. There is one longitudinal interventional study in 198 Japanese aged 65–84 years, which showed that maintenance of a physically active lifestyle over 1 year with a step count of 6,600 steps/day and/or a total activity duration of 16 min/day at moderate-to-vigorous intensity was significantly associated with lower stiffness of central arteries compared with less active persons [23]. This has so far not been shown in a population-based longitudinal cohort study such as SAPALDIA.

The significant sex difference in baPWV is supposed to reflect the cardio-protective effect of hormonal levels, especially oestrogen through vasodilation and reduction of vascular tone [24]. Oestrogen enhances nitric oxide production by stimulation of endothelial nitric oxide synthase stimulation inducing vasodilation as the main suggested pathway [25]. Besides, oestrogen has been beneficially linked with reductions in blood pressure and deceleration of age-associated arterial stiffness in postmenopausal women [26]. It is suggested that the effect of oestrogen is influenced by age, with lower protective effect of oestrogen on the vasculature with longer time from menopause due to lower levels of oestrogen and number of oestrogen receptors [27]. The mostly postmenopausal females of our study population showed beneficial associations of long-term PA with arterial stiffness. The effect estimates were not significantly different between supposedly pre- and postmenopausal women, when taking into account age in SAPALDIA 2 and 3. Nevertheless, the inconsistent results within the females becoming active compared with males need further investigation.

Longevity has been found to be strongly associated with a healthy lifestyle in a population-based prospective study in

males with a mean age of 72 years [28]. Accordingly, in this study, older males with sufficient PA had an almost 30% lower mortality risk and a probability of 54% to live up to the age of 90 years if they were also non-smokers, non-diabetic, normotensive and had a normal weight profile at the age of 70 years. Furthermore, a recent systematic review has shown that an increase in baPWV by 1 m/s is not only associated with increased risk of CV events and CV mortality (12 and 13%, respectively), but also with a 6% increase in all-cause mortality [14]. Building on this, our study results strengthen the evidence that adoption of a physically active lifestyle has the potential to beneficially influence the vasculature in terms of lower arterial stiffness also in later life. This may reduce the risk of CV disease also in older adults having become physically active later in life, with positive effects on mortality and longevity.

Some study limitations need to be considered. Arterial stiffness measurement was only available in SAPALDIA 3. PA has not been assessed objectively because of logistic and financial reasons. However, the used short questionnaire is a valid instrument for population-wide PA assessments [18]. Attrition and selection bias might have affected the analyses, since only persons with full data on PA, arterial stiffness and co-variates were included in this study. However, the analysed sample was not different on average in terms of baPWV, BMI, mean arterial pressure and vigorous PA compared with the rest of the SAPALDIA 3 sample. The analysed sample was significantly older, smoked more and had lower mean arterial pressure and more moderate PA.

Conclusions and implications

In summary, this is the first longitudinal population-based cohort study showing that keeping up or adopting a physically active lifestyle was associated with lower arterial stiffness in older adults after a follow-up of almost a decade. These findings represent a useful basis for generating hypothesis that should be tested in large randomised controlled trials concerning the long-term effects and underlying pathways of PA, exercise training and long-term change towards a physically active lifestyle on arterial stiffness in older adults.

Key points

- Long-term physical activity was associated with reduced arterial stiffness.
- Adopting a physically active lifestyle was beneficial regarding arterial stiffness and cardiovascular risk also in older adults.
- RCTs on the long-term effects and underlying pathways of physical activity on arterial stiffness in older adults are recommended.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Conflicts of interest

None declared.

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Supplementary material: Appendix 1

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(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics

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Chapter 7

Main Results

Chapter 7 Main Results

7.1 Aim 1: Measuring Characteristics of Arterial Stiffness Indices (CAVI, baPWV) in a Caucasian Cohort

The first aim of the PhD thesis was to determine the measuring characteristics in terms of the reproducibility of the novel arterial stiffness measures CAVI and baPWV in Caucasians aged at least 50 years of the SAPALDIA cohort. These two arterial stiffness indices are derived from an oscillometric measurement with the VaSera VS-1500N vascular screening system. This work resulted in one publication in the Scandinavian Journal of Clinical & Laboratory Investigation showing the high reproducibility of these indices.[1] The mean coefficient of variation for CAVI was 4.4% and for baPWV 3.9%. The intraclass correlation coefficient was 0.8 for CAVI and 0.9 for baPWV. The mixed linear model revealed that 68.7% of the CAVI and 80.1% of the baPWV variance was accounted for by the subject, 5.2%/8.1% by the fieldworker, 6.7%/7.8% by variation between measurement days, and 19.4%/4% by measurement error. Bland-Altman plots showed no particular dispersion patterns. This could be shown for the first time in a representative subsample of a Caucasian cohort, since both of these newly emerging arterial stiffness indices reflecting early CVD risk have so far mainly been studied in Asian populations[56] or only in small studies with Caucasians.[91] Valid markers of CVD are essential and highly important for CVD risk stratification on the population level.

Furthermore, we have analyzed associations of CAVI and baPWV with age and sex as the main determinants of arterial stiffness in the SAPALDIA cohort to prove the high quality of these indices. CAVI and baPWV linearly increased with age, CAVI on average by 0.9 per decade and baPWV by 1.8 m/s. Statistically significant gender differences were observed for CAVI in the age groups 60-69 and 70-81 years and for baPWV in the age groups 50-59 and 60-69 years, with lower values among women. These results could be integrated in the second manuscript published in the European Journal of Epidemiology.[2]

7.2 Aim 2: Cross-Sectional Association of Physical Activity and Arterial Stiffness

In the second aim we focused extensively on analyzing associations between physical activity and arterial stiffness in the SAPALDIA cohort of older adults from a cross-sectional point of view. During the data collection of SAPALDIA 3 the IPAQ has been consulted to classify the subjects' physical activity level. We hypothesized that insufficient physical activity is associated with increased arterial stiffness assessed by CAVI and baPWV. We found that in

this general Caucasian population of older adults higher levels especially of vigorous physical activity were associated with lower arterial stiffness reflecting lower cardiovascular risk. After adjustment for several confounders moderate, vigorous and total physical activity were inversely associated with CAVI. baPWV showed negative and marginally significant associations with vigorous and moderate physical activity, but not with total physical activity. Increased arterial stiffness (CAVI ≥ 9, upper tertile) was inversely and significantly associated with vigorous physical activity (odds ratio (OR) = 0.65, 95% confidence interval (CI) 0.48–0.88), and marginally significantly with total physical activity (OR 0.76, 95% CI 0.57–1.02) and moderate physical activity (OR 0.75, 95% CI 0.56–1.01). The odds ratio for baPWV ≥ 14.4 m/s was 0.67 (95% CI 0.48–0.93) across the vigorous physical activity levels, and was non-significant across the total (OR 0.91, 95% CI 0.66–1.23) and moderate physical activity levels (OR 0.94, 95% CI 0.69–1.28). These data support the importance of physical activity for improving cardiovascular health in older adults. These results have been published in the European Journal of Epidemiology.[2]

7.3 Aim 3: Longitudinal Association of Physical Activity and Arterial Stiffness

To add on this from a longitudinal point of view we have extensively worked on the third aim of this PhD thesis analyzing the association between change in physical activity between the first and second follow-up of SAPALDIA (SAPALDIA 2 to 3) and CVD risk using baPWV as marker in multilevel models including several confounding factors. We hypothesized that an increase in physical activity between SAPALDIA 2 and 3 was associated with lower cardiovascular risk assessed by arterial stiffness. This is the first longitudinal population based cohort study showing that keeping up or adopting a physically active lifestyle was associated with lower arterial stiffness in older adults after a follow-up of almost a decade. In the entire study population adjusted means of baPWV were significantly lower in persons with sufficient moderate-to-vigorous physical activity a) in SAPALDIA 2 but not SAPALDIA 3 and b) in both surveys when compared to persons with insufficient physical activity in both surveys. In sex specific analyses it has been shown that in sufficiently active males and females in both surveys baPWV was lower compared to insufficiently active persons. Besides, the fully covariate-adjusted means of baPWV were significantly lower in men becoming active (13.8 m/s, P=0.04) compared to men remaining inactive (14.3 m/s), whereas significantly lower in females with sufficient physical activity in SAPALDIA 2 but not in SAPALDIA 3 (13.6 m/s, P=0.02) compared to females remaining inactive (13.9 m/s).

Increasing the proportion of older adults adhering to physical activity recommendations incorporating also vigorous physical activity may have a considerable impact on vascular health at older age and may contribute to healthy ageing in general. These findings will strengthen physical activity recommendations within CVD prevention guidelines in older adults with respect to the prevention of manifest CVD and related health outcomes. A manuscript presenting these findings has been published in the journal Age and Ageing.[3]

Chapter 8

Discussion and Synthesis

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This PhD thesis has been conducted to analyze of the association between physical activity assessed by the IPAQ and a short physical activity questionnaire as a preventive life style component of aggressive decrease of atherosclerotic modifiers (ADAM)[55] and arterial stiffness in a Caucasian cohort aged at least 50 years (N=3026). We have found that physical activity is cross-sectionally and in the long-term beneficially associated with arterial stiffness and, thus, lower cardiovascular risk. In this cohort of older adults a physically active lifestyle incorporating vigorous physical activity may have a significant effect on population health. The analyses have been based on the evaluation of the measuring characteristics of the oscillometric arterial stiffness indices CAVI and baPWV for the first time performed in a Caucasian cohort. We have shown that CAVI and baPWV are highly reproducible and easy-to-apply for cardiovascular risk assessments in Caucasians.

8.1 Aim 1: Measuring Characteristics of Arterial Stiffness Indices (CAVI, baPWV) in a Caucasian Cohort

The reproducibility of clinical measurements is an essential and crucial feature for clinical and scientific use. The reproducibility of the arterial stiffness indices CAVI and baPWV has so far only been shown in Asian populations[75,86,88] and in a small study with Caucasians (N=7).[91] Therefore we have evaluated the reproducibility of CAVI and baPWV in a representative subsample of the SAPALDIA 3 cohort of Caucasian adults aged 50-81 years. We could show that both CAVI and baPWV are highly reproducible arterial stiffness indices also in a Caucasian population. The methodology is applicable for large clinical trials or cohort studies. The peripheral augmentation index simultaneously assessed with the VaSera vascular screening system had distinct lower reproducibility. These results show that CAVI and baPWV are reliable and easy-applicable non-invasive vascular biomarkers of arterial stiffness that can be used for population wide cardiovascular screening. The extensive statistical analyses besides the large representative sample of a cohort is a major strength of this reproducibility study compared to other studies using mostly the coefficient of variation as a statistical measure of reproducibility.[75,88,91] We could confirm the high reproducibility by using intraclass correlation coefficients and Bland-Altman-plots. Furthermore, the high proportion of variance on account of the subject within the mixed model (CAVI, 68.7%; baPWV, 80.1%) shows that most of the measurement variance of these indices is due to subject specific characteristics. Since, in addition, the fieldworker effect was small with 5.2%

of the CAVI variance and 8.1% of baPWV we can conclude that arterial stiffness measurement with the VaSera VS-1500N screening system has limited need for fieldworker training in a standardized setting and is highly reproducible. This is mainly because CAVI and baPWV measurement involves basic clinical devices (blood cuffs, electrocardiogram leads, phonocardiogram), which makes it easily applicable also for large scale CVD risk assessments or routine screenings in Caucasian populations.

8.2 Aim 2: Cross-Sectional Association of Physical Activity and Arterial Stiffness

The second aim of this PhD thesis was targeted at the analyses of the cross-sectional association between physical activity and arterial stiffness reflecting CVD risk in multilevel models including several confounding factors. Physical activity is regarded as an important health promotion measure with protective impact on the cardiovascular system and, thus, as one component of aggressive decrease of atherosclerotic modifiers (ADAM).[55] The main focus of the second aim was the question how a physically active lifestyle is cross-sectionally associated with arterial stiffness in the SAPALDIA cohort. Up-to-date this question has been insufficiently studied in older adults in population based studies. Furthermore, there is no comparable cohort in which a measure of arterial stiffness could be analyzed in association with a detailed questionnaire of physical activity like the IPAQ. We found that adjusted for several potential confounders higher levels of physical activity are associated with lower cardiovascular risk in terms of lower arterial stiffness measured with CAVI and baPWV. Thereby, the strongest associations were evident for higher amounts of physical activities performed with more vigorous intensity. These results support the importance of physical activity for improving cardiovascular health in older people and suggest that vigorous physical activity promotion in this age group may prevent against increased arterial stiffness resulting from atherosclerotic modifications.

Our study results are in line with other cross-sectional analyses that have, however, used cfPWV as an outcome.[99,100] Since arterial stiffness is differently affected by physical activity across the arterial tree,[98,101] our study adds significant novel evidence concerning the beneficial association of physical activity with mixed measures (central and peripheral) of arterial stiffness (CAVI and baPWV). Our study results are also in agreement with the current state of research of intervention studies concerning this topic and provide scientific support from a population study perspective. Two systematic reviews have recently shown that aerobic exercise especially at higher intensities beneficially affects arterial stiffness.[95,96]

CAVI and baPWV did not show fully agreeing results concerning their association with levels of moderate, vigorous and total physical activity. Even if the tendencies of both outcome associations point to consistent conclusions toward lower arterial stiffness with more physical activity, the disagreement needs further investigation. CAVI and baPWV are currently used as combined measures of central and peripheral arterial stiffness.[77,114] Since CAVI also correlated well with intima media thickness (IMT) and plaque score (still pending for Caucasians) reflecting carotid and coronary atherosclerosis, CAVI is suggested to represent systemic arterial stiffness.[115] Very recently CAVI has been shown to be associated with carotid atherosclerosis similar to cfPWV and baPWV in 500 Caucasians aged 35-74 years.[116] CAVI and baPWV have been proven to be valid vascular biomarkers for non-invasive arterial stiffness assessment associated with cardiovascular disease risk and outcomes,[62,115,117,118] and with central arterial stiffness.[74,83] Despite, the interpretation of the results concerning the association between physical activity and arterial stiffness has to be performed against the background that the effect of physical activity on arterial stiffness varies across the arterial tree.[98,101] Furthermore, CAVI is derived from PWV measurements, by using a mathematical transformation with inclusion of the stiffness parameter β and a modification of the Bramwell-Hill equation.[75] These methodological differences of CAVI and baPWV should be investigated in more detail in view of associations with physical activity.

8.3 Aim 3: Longitudinal Association of Physical Activity and Arterial Stiffness

Within aim 3 we have found that long-term maintenance or adoption of a physically active lifestyle in a Caucasian cohort of adults aged 50-81 years was associated with lower arterial stiffness after almost a decade. These results strengthen the cross-sectional analyses and support the finding that physical activity is cross-sectionally and longitudinally beneficially associated with arterial stiffness in the general Caucasian population of older adults and, thus, with decelerated vascular ageing and lower cardiovascular risk. This has so far not been shown in a comparable population based cohort such as SAPALDIA. Our result is of particular interest since arterial stiffness is progressively increasing with age. Furthermore, it is important to show this beneficial association of physical activity with arterial stiffness in older adults, because it can be assumed that with ageing structural and functional components of the arteries are less susceptible to beneficial modifications such as decelerated stiffening as presented in our study population or to positive effects on vascular endothelial dysfunction.[119] The found association between physical activity and arterial

stiffness was present in males and females concerning the comparison between remaining active individuals from SAPALDIA 2 to 3 with individuals remaining inactive. Beyond that and in contrast to the cross-sectional analyses without sex specific associations, there were differences between males and females in the longitudinal analyses: Female individuals becoming inactive and male individuals becoming active in SAPALDIA 3 had also significantly lower arterial stiffness in SAPALDIA 3. This finding points to the assumption that a physically active lifestyle at any point in life has a beneficial effect on arterial stiffness later in life. In older adults there is only one longitudinal study over one year in 198 Japanese aged 65-84 years similarly showing a beneficial association of higher levels of moderate-to-vigorous physical activity of at least 16 min/day compared to inactive individuals with stiffness of central arteries.[98] This is very comparable to the 15 min/day of moderate intensity physical activity found to be associated with 14% reduced mortality risk.[22] In our study population individuals remaining active had a median of 61 min/day more moderate-to-vigorous physical activity compared to individuals remaining inactive (median 0 min/day). Even if these results are not fully comparable due to different outcomes and methodological inconsistencies further investigations are warranted to shed light on the differences in the amount of moderate-to-vigorous physical activity and its association with arterial stiffness in the long-term.

Both the IPAQ for extensive physical activity assessment and the arterial stiffness measurements by CAVI and baPWV have been applied for the first time in SAPALDIA within the second follow-up. The promising results of this beneficial cross-sectional association of physical activity with arterial stiffness have the major potential of being baseline findings for longitudinal arterial stiffness outcome analyses with the change of physical activity assessed with IPAQ in different intensities and domains as primary predictor in the third follow-up (SAPALDIA 4). These upcoming analyses will shed more light on the associations between physical activity and cardiovascular risk and target organ damage in a highly representative population based cohort of ageing adults.

This PhD thesis focused on arterial stiffness and vascular ageing in view of physical activity or more so physical inactivity or sedentary behavior as a potential risk factor. Within this context the EVA-ADAM concept by Nilsson et al. sets the framework for physical activity potentially being one aggressive decrease of atherosclerotic modifier (ADAM) targeted at early vascular ageing (EVA).[55] A quote by the physician Sir William Osler from 1898

underlines the importance of lifelong vascular health on the basis of genetic determinants and lifestyle influences for healthy ageing in terms of longevity:

> *"Longevity is a vascular question, which has been well expressed in the axiom that man is only as old as his arteries. To a majority of men death comes primarily or secondarily through this portal. The onset of what may be called physiological arterio-sclerosis depends, in the first place, upon the quality of arterial tissue which the individual has inherited, and secondly upon the amount of wear and tear to which he has subjected it."* (Sir William Osler, 1898)[120]

Physical activity and exercise training are nowadays regarded as lifestyle components with potential beneficial effects on vascular ageing and stiffening and reduction of cardiovascular risk.[15–18,94,121] Especially aerobic exercise as an intentional and structured unit of physical activity has been recently highlighted as a "'first line' strategy for prevention and treatment of arterial ageing and a vital component of a contemporary public health approach for reducing the projected increase in population CVD burden."[122] On the molecular basis this may be due to reductions in oxidative stress, fibrosis and advanced glycation end-products, and maintenance of endothelial function and nitric oxide bioavailability.[122] From this perspective, the physical activity-arterial stiffness relationship may positively contribute to the beneficial association between physical activity and longevity. In this regard, longevity has been proven to be strongly associated with a healthy lifestyle in a population based prospective study (males, mean age 72 years).[123] Thereby, older adults with sufficient physical activity according to current guidelines had an almost 30% lower mortality risk and a probability of 54% to live up to the age of 90 years if they were also non-smoker, and had a normal diabetic, hypertonic and weight profile at the age of 70 years. In a recent large pooled cohort analysis from six prospective cohorts in 654'827 adults aged mostly at least 40 years it was found that after a median follow-up of 10 years a minimum amount of light intensity physical activity in terms of up to 75 minutes of brisk walking per week was associated with a 1.8 years longer life expectancy compared to inactive individuals.[124] Similarly, adhering to current physical activity recommendations was associated with 3.4 years of longer life expectancy, increasing up to 4.2 years in individuals with approximately 300 minutes of moderate intensity physical activity (e.g. brisk walking). Adding to this, our study results strengthen the importance of a physically active lifestyle also in older adults with significant beneficial effects on the CVD risk and healthy vascular ageing potentially positively contributing to longevity. Further investigations are recommended focusing on the interrelations of physical activity with arterial stiffness and longevity, since arterial stiffness

represents a measure of the cumulative effect of cardiovascular risk factors such as insufficient physical activity on the vasculature with ageing.[55] Up-to-date, there are no longitudinal cohort study results concerning physical activity, arterial stiffness and longevity in ageing populations.

8.4 Strengths and Limitations

A major strength of this PhD thesis is that the data are derived from a nearly 25 year prospective population based Swiss cohort meeting highest standards of data collection and data management. Therefore, the performed association analyses are related to a detailed characterized Caucasian cohort with the possibility to control for several potential confounders. Based on this the study population of this PhD thesis is large enough to give highly relevant conclusions for public health. The IPAQ used for the physical activity assessment is a cross-national monitoring tool of physical activity for adults and has been shown to be a feasible, reliable and valid measurement instrument of physical activity in several countries.[105] From this it follows that the produced data are easily comparable to other cohorts studying physical activity. The IPAQ not only allows duration and intensity but also domain related analyses of physical activity and, thus, gives the opportunity to study physical activity behavior in more detail. There is no other Caucasian cohort of older adults providing population based data on the association between long-term change in physical activity and oscillometrically measured arterial stiffness.

At this point also some study limitations need to be considered. Even if the IPAQ is a valid instrument for population wide physical activity monitoring, it is a subjective method and is prone to over-estimation of physical activity especially in adults aged ≥65 years. However, it has been shown that vigorous physical activities are less affected by this reporting bias also in older adults,[125] which showed the strongest association with arterial stiffness in this PhD thesis. Objective physical activity measurements such as accelerometer are increasingly used in research. However, logistic and financial reasons have not allowed implementing such objective measures of physical activity in the large sized cohort study SAPALDIA. Due to the same reason the reproducibility study of CAVI and baPWV could not be performed in comparison to the gold-standard measurement cfPWV. As pointed out in the publication[1] the reproducibility expressed as coefficient of variation of CAVI and baPWV is very comparable to cfPWV. Arterial stiffness has been measured for the first time in the second follow-up of SAPALDIA, wherefore longitudinal outcome analyses of the change of physical

activity on the change of arterial stiffness from SAPALDIA 2 to 3 could not be performed. Selection and healthy survivor bias might have affected the analyses, since only persons with full data on physical activity, arterial stiffness and covariates were included in this PhD thesis. Yet, the analyzed sample was not significantly different in the main variables of interest compared to the total SAPALDIA cohort.

8.5 Significance and Conclusions

This PhD thesis addresses one of the main questions in health-enhancing physical activity and public health research, which are the associations of chronic physical activity with the pathophysiologic processes underlying cardiovascular morbidity and mortality. In view of the world-wide research on CVD and health promotion measures, a highly important public health impact of this study may arise from the usage of oscillometrically measured arterial stiffness indices such as CAVI and baPWV as early, subclinical arteriosclerosis markers and the exploration of potential risk factors such as physical inactivity. Risk stratification is essential for goal-oriented and population wide primary and secondary prevention. Early detection of CVD and cardiovascular risk factors is crucial besides promotion of prevention and early treatment for diminishing the increasing public health and economic impact of CVD. This PhD thesis significantly contributes to the understanding of the association of physical activity as an anti-atherosclerotic modifier with arterial stiffness and, thus, CVD risk. Physical activity assessed with the long version of the IPAQ offered the unique opportunity to analyze the association with arterial stiffness down to intensity and duration as well as energy expenditure of physical activity. For the first time we have been able to show that a long-term physically active lifestyle over a period of almost a decade or the adoption of more physical activity especially of vigorous intensity is associated with lower arterial stiffness and, therefore, lower cardiovascular risk in middle-aged and older adults. In conclusion this PhD thesis adds highly significant evidence to an up-to-date public health research question to that effect that increasing the proportion of older adults adhering to physical activity recommendations incorporating also vigorous physical activity may have a considerable impact on vascular health in ageing populations and may contribute to healthy ageing in general.

Chapter 9

Perspectives

Chapter 9 Perspectives

In the following chapter three projects will be put in perspective to this PhD thesis that are all highly relevant for upcoming analyses.

9.1 Associations of Physical Activity with Central Arterial Stiffness and Hemodynamics

Central arterial (aortic) stiffness and central hemodynamics are considered to be important determinants of improved cardiovascular risk stratification with major potential for public health related examinations.[15,126] This is because central hemodynamic indices reflect the true load of genetic and lifestyle influences on inner organs and the vascular system.[8] Due to the amplification of the pressure waveform propagating along the arterial tree on the basis of reflections and increasing arterial stiffness in the periphery central blood pressure cannot be inferred by peripheral blood pressure.[15] Central systolic blood pressure varies extensively from brachial systolic blood pressure and also within one individual at all age groups.[127] Against this background growing evidence has accumulated in recent years suggesting that central blood pressure may be a better predictor of cardiovascular risk and future cardiovascular events compared to brachial blood pressure and may reduce hypertension misclassification.[128] It is for this reason that besides invasive methods for assessing central hemodynamics and aortic stiffness, unsuitable for population examinations, non-invasive methods such as applanation tonometry and transfer functions for estimations on the basis of peripheral pressures have been developed and validated.[15,127] Transfer functions based on oscillometric measurements of brachial blood pressure have the advantage of being less operator dependent compared to tonometer assessments at the carotid.[127] Building on this we have analyzed the feasibility of the ARCSolver algorithm[109] to retrospectively derive central hemodynamics and aortic stiffness parameters from cuff-based blood pressure measurements. This has been done in cooperation with the working group of Dr. S. Wassertheurer (Cardiovascular Diagnostics, AIT Austrian Institute of Technology GmbH) in a separate study (N=68, mean age 51±18 years) based on a dataset of a previous study.[91] The ARCSolver method is a mathematical procedure for the calculation of aortic stiffness and central hemodynamic measures from peripheral pulse waves and blood pressure measurements at the brachial artery using a common occlusive cuff.[109] The ARCSolver algorithm has been validated invasively and non-invasively.[129–131] Within this work we could show that it is feasible to retrospectively apply the ARCSolver algorithm to oscillometrically

measured pulse wave signals in order to derive aortic stiffness and central hemodynamics. These promising results have been published in the journal Blood Pressure Monitoring (see Appendix B).[110] This successful work is the basis for upcoming analyses of aortic stiffness and central hemodynamics in SAPALDIA. It opens the perspective for promising future outcome and association analyses within this very well characterized cohort and beyond in other studies. Thereby it will be of specific interest to analyze whether and how physical activity is cross-sectionally and a physically activity lifestyle in the long-term is associated with central hemodynamics and aortic stiffness in older adults.

9.2 Domain-Specific Associations of Physical Activity with Arterial Stiffness and Hemodynamics

Furthermore, as pointed out by Hallal et al. domain specific analyses of physical activity are highly important to support public health actions in view of increasing physical activity and decreasing sedentary behavior.[9] The IPAQ applied in SAPALDIA 3 assesses physical activity domain specifically: leisure time, domestic and gardening activities, work-related, transport-related. This will allow us to analyze associations of physical activity performed in different domains with central and peripheral hemodynamics and arterial stiffness. Thereby, for example the question will be of interest whether active transportation in comparison to leisure time physical activity has the potential of being beneficially associated with lower cardiovascular risk.

9.3 Air Pollution as a Modifier of the Association Between Physical Activity and Arterial Stiffness/ Hemodynamics

As highlighted in the introduction, environmental influences are highly important determinants of physical activity,[27] with air pollution being the main environmental determinant being studied in SAPALDIA using high quality, Swiss wide data.[103,104] Both, high amounts of physical activity and low air pollution exposure are recommended by several global health institutions for the prevention of cardiovascular disease.[5,94,132,133] Strong epidemiologic evidence exists suggesting that air pollution is negatively associated with cardiovascular mortality and morbidity.[132,134] Short and long-term air pollution exposure is linked with coronary artery disease, heart failure and stroke.[132] A very recent expert position paper points out the high importance of the associations between air pollution, CVD and global health.[132] Subclinical vascular modifications are thought to mediate in part the pathophysiological effect of air pollution on CVD.[132] In this connection mainly atherosclerosis

measured as carotid-intima media thickness has been studied.[132] However, atherosclerosis is closely related to stiffening of the arteries in the initial stage.[50] Up-to-date associations between air pollution and arterial stiffness have been insufficiently studied in themselves[135] and were never studied in the context of chronic physical activity and different physical activity domains. Studying the interaction between physical activity and air pollution is not only justified from the perspective of physical activity recommendations in different environmental contexts, but is also justified against the current biological understanding of physical activity and air pollution effects on atherosclerotic pathophysiology. Both, physical inactivity and air pollution have been associated with systemic low grade inflammation and oxidative stress, both risk factors for endothelial dysfunction, atherosclerosis and CVD.[133,136] Physical inactivity[7] and air pollution[133,137] are both positively associated with blood pressure increase. In addition there is synergy at the level of pathophysiology, because physical activity leads to a higher and potentially deeper inhalation of air pollutants through elevated breathing rates, which could elevate local respiratory and systemic inflammation.[138,139] Nevertheless, being physically active compared to resting in a polluted environment was found to be associated with lower systolic blood pressure regardless of the level of pollution.[140] In contrast, short-term exposure to traffic-related air pollution through physical activity was negatively associated with arterial stiffness in a small experimental study.[141] Besides, in a cross-over study among 53 healthy women exposure to traffic-related air pollution through cycling activity led to an acute increase in systolic blood pressure.[142] Apart from these studies, the associations between physical activity and air pollution have so far mainly been studied concerning lung function and exercise performance, and there is limited evidence concerning interactions with the cardiovascular system.[143] Despite presenting several severe cardiovascular risks associated with acute and long-term air pollution exposure a current expert position paper recommends physical exercise and being physically active together with avoiding major traffic roads.[132] However, there is lack of evidence on how the associations between physical activity performed in different domains of daily living and cardiovascular risk markers especially concerning aortic stiffness and central hemodynamics are modified by air pollution on the population level. Therefore, in upcoming analyses building on this PhD thesis we will focus on the research question whether and how physical activity recommendations need to be refined towards the prevention of atherosclerosis and CVD by a) studying cross-sectional and longitudinal associations of

different physical activity domains (e.g. leisure time vs. transport-related physical activity) with central and peripheral arterial stiffness and hemodynamics including aortic stiffness derived with a novel transfer algorithm (ARCSolver) on the population level, and by b) assessing modifying effects of air pollution on the physical activity/ arterial stiffness/ hemodynamics associations towards context and environment specific physical activity recommendations. Thereby it will be of interest whether the respiratory and cardiovascular health state influences the association between chronic physical activity and cardiovascular risk markers and the potential modification by long-term ambient and traffic-related air pollution.

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Appendix A

Publication: Review of Exercise Interventions & Arterial Stiffness

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REVIEW ARTICLE

Aerobic, resistance and combined exercise training on arterial stiffness in normotensive and hypertensive adults: A review

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Abstract
Exercise training has different effects on arterial stiffness according to training modalities. The optimal exercise modality for improvement of arterial function in normotensive and hypertensive individuals has not been well established. In this review, we aim to evaluate the effects of aerobic, resistance and combined aerobic and resistance training on arterial stiffness in individuals with and without hypertension. We systematically searched the Pubmed and Web of Science database from 1985 until December 2013 for relevant randomised controlled trials (RCTs). The data were extracted by one investigator and checked by a second investigator. The training effects on arterial stiffness were estimated using weighted mean differences of the relative changes (%) with 95% confidence intervals (CIs). We finally reviewed the results from 17 RCTs. The available evidence indicates that aerobic exercise tends to have a beneficial effect on arterial stiffness in normotensive and hypertensive patients, but does not affect arterial stiffness in patients with isolated systolic hypertension. Resistance exercise has differing effects on arterial stiffness depending on type and intensity. Vigorous resistance training is associated with an increase in arterial stiffness. There seem to be no unfavourable effects on arterial stiffness if the training is of low intensity, in a slow eccentric manner or with lower limb in healthy individuals. Combined training has neutral or even a beneficial effect on arterial stiffness. In conclusion, our review shows that exercise training has varying effects on arterial stiffness depending on the exercise modalities.

Keywords: *Exercise, cardiovascular, health, ageing, lifestyle*

Introduction

Arterial stiffness is as an emerging biomarker in the assessment of vascular health (Laurent, Alivon, Beaussier, & Boutouyrie, 2012). Arterial stiffness increases with advancing age in healthy normotensive adults (Vaitkevicius et al., 1993) and hypertensive patients (London, Marchais, & Safar, 1989). Large artery stiffening is independently associated with cardiovascular events and all-cause mortality (Karras et al., 2012; Vlachopoulos, Aznaouridis, & Stefanadis, 2010; Vlachopoulos, Aznaouridis, Terentes-Printzios, Ioakeimidis, & Stefanadis, 2012). Hypertension has become the leading cause of cardiovascular disease and all-cause mortality (Chow et al., 2013; Danaei et al., 2011; Kearney et al., 2005). The relationship between hypertension and arterial stiffness may be bi-directional (Franklin, 2005). In contrast to conventional understanding, a recent study showed that aortic stiffness may be a precursor of hypertension, rather than being the result of high blood pressure (Kaess et al., 2012). Given that arterial stiffness is a precursor of hypertension, lowering blood pressure alone is not enough to decrease cardiovascular risk. Therefore, lifestyle modifications aiming at the reduction of arterial stiffness are of great clinical importance.

Exercise training is an important component of lifestyle modification. There are two major types of exercise, aerobic and resistance exercise training. Aerobic exercise training has been defined by the American College of Sports Medicine (ACSM) as any activity that involves major muscle groups and is continuous and rhythmical in nature (Garber et al., 2011). Resistance exercise training is defined as any activity that involves brief, repeated execution of voluntary muscle contractions against a load that is

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greater than those normally encountered in activities of daily living (Lee & Carroll, 2007).

Although the blood pressure lowering effect of exercise training has been widely accepted (Cornelissen & Smart, 2013), the effect of exercise training on the vascular system is not fully clarified. Previous studies showed that an active lifestyle with regular physical activity is associated with reductions in cardiovascular disease risk in healthy individuals and patients with cardiovascular disease (Hakim et al., 1999; Mons, Hahmann, & Brenner, 2014; Sesso, Paffenbarger, & Lee, 2000). However, the extreme daily strenuous physical activity may increase cardiovascular mortality in patients with coronary heart disease in a reverse J-shaped association (Mons et al., 2014).

When examining the time course of exercise-induced change on vasculature, shear stress flow-mediated vasodilatation (FMD) was initially altered, followed by other functional and structural adaptations. Arterial compliance is the ability of an artery to expand and recoil during cardiac contraction and relaxation, while arterial stiffness is the inverse (Nichols, O'Rourke, Hartley, & McDonald, 1998). Arterial stiffness is determined by the functional (endothelium, smooth muscle cells) and structural components (elastin, collagen and connective tissue). It is a function of the structure of an artery and may be modified more rapidly or slowly depending on which component is influenced by exercise training (Green et al., 2013; Green, Spence, Halliwill, Cable, & Thijssen, 2011; Tinken et al., 2010). However, the studies investigating the effect of exercise training on arterial stiffness were less uniform. Previous cross-sectional studies showed that aerobic training is associated with improved arterial stiffness (Otsuki et al., 2006; Sugawara et al., 2006; Tanaka et al., 2000), whereas resistance training is associated with an increase of arterial stiffness (Bertovic et al., 1999; Miyachi et al., 2003; Otsuki et al., 2006). However, the combination of aerobic and resistance training in rowers showed either no change (Kawano et al., 2012; Petersen et al., 2006) or improved arterial stiffness (Cook et al., 2006). These cross-sectional studies showed inconsistent results, but they do not suggest cause and effect between exercise and the change of arterial stiffness. Conclusive explanations for the underlying mechanisms are still lacking and the true relationship should be further analysed and confirmed in randomised controlled trials (RCTs). Thus, the aim of this review is to summarise the current evidence based on RCTs regarding the effect of exercise training with a duration >4 weeks on arterial stiffness in normotensive and hypertensive individuals.

Methods

Search methods

We systematically searched for RCTs investigating the effect of exercise training on arterial compliance published from 1985 to December 2013 in the PubMed and Web of Science database. Search terms included "aerobic training" OR "endurance training" OR "resistance training" OR "strength training" OR "weight training" OR "eccentric training" OR "concentric training" OR "exercise" AND "vascular stiffness" OR "arterial stiffness" OR "arterial compliance" OR "arterial stiffening". Abstract, case reports and articles not in English were not considered. The reference lists of published articles and reviews on the topic were checked to identify other eligible studies.

Criteria for study selection

Definition of hypertension. The definition of hypertension is based on recommendations by the American Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. According to the JNC-7 report (2003): prehypertension is defined as SBP ranging from 120–139 mmHg and/or DBP 80–89 mmHg. Hypertension is defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg. Isolated systolic hypertension (ISH) is defined as an elevated SBP of >140 mmHg with a normal (<80 mmHg) DBP (Chobanian et al., 2003).

Types of studies

We included RCTs that involved a non-exercise control group (parallel design) or a non-exercise control phase (cross-over design). The study subjects enrolled should be either healthy normotensive individuals or hypertensive patients without any significant comorbidities.

Types of interventions

RCTs prescribing aerobic or resistance or combined exercise training of at least 4 weeks were included as follows: (1) Aerobic exercise versus non-exercise control group/phase; (2) Resistance exercise versus non-exercise control group/phase; (3) Combined exercise (aerobic exercise plus resistance exercise) versus non-exercise control group/phase; (4) Aerobic, resistance exercise versus non-exercise control group/phase; (5) Aerobic, combined exercise versus non-exercise control group/phase; (6) Resistance, combined exercise versus non-exercise control group/phase; (7) Aerobic, resistance, combined exercise versus non-exercise control group/phase.

Types of outcome measures

There are various techniques for assessing arterial stiffness. We included studies using regional and local arterial stiffness measured as primary or secondary outcome in our review. In particular these were as follows: central arterial stiffness measured as carotid-femoral pulse wave velocity (cfPWV), carotid arterial compliance and carotid β-stiffness index; peripheral arterial stiffness measured as carotid-radial pulse wave velocity (crPWV), femoral-ankle pulse wave velocity (faPWV), femoral-dorsalis pedis pulse wave velocity (fdPWV); systemic arterial stiffness measured as brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI). Standardised reference values have recently been published by the "Reference Values for Arterial Stiffness Collaboration" (Mattace-Raso et al., 2010). A higher value of pulse wave velocity, β-stiffness index, CAVI or lower value of arterial compliance denotes a stiffer artery. An increase in cfPWV and baPWV by 1 m/s has been shown to increase cardiovascular mortality by 15% (Vlachopoulos et al., 2010) and 13% (Vlachopoulos et al., 2012), respectively.

Quality assessment

The quality of the included studies was assessed using the Jadad scale (Jadad et al., 1996), giving one point each for descriptions of randomisation, blinding, dropouts and appropriateness of randomisation and blinding. Blinding of the investigator administering the intervention and of the participants performing the exercise is almost impossible in exercise intervention trials. Therefore, the Jadad scale was slightly modified by giving one point for proper blinding of the outcome assessor. Since all studies had to be RCTs according to the inclusion criteria, the range of the Jadad score for the included studies in this review was one to five, with higher scores reflecting superior quality.

Data extraction

The following data were extracted: first author, year of publication, type of study design, characteristics of the study population (health status, age, sex), training programme (duration, frequency, intensity), study sample size, parameters of arterial stiffness, intervention effects (weighted mean difference of relative change with a 95% CI) and Jadad score. The training intensity of aerobic exercise was indicated as heart rate reserve (HRR), maximum heart rate (HR_{max}) or maximal oxygen consumption (VO_{2max}). The intensity of aerobic exercise was defined as follows: moderate, 40–59% heart rate reserve = 64–76% maximal heart rate = 46–63% maximal oxygen uptake; vigorous, 60–89% heart rate reserve = 77–95% maximal heart rate = 64–90% maximal oxygen uptake (Garber et al., 2011). The training intensity of resistance exercise was indicated as a percentage of 1 RM (one repetition maximum). The intensity was defined as follows: light, < 50% 1RM; moderate, 50–69% 1RM; vigorous, 70–84% 1RM (Garber et al., 2011). The primary outcome was resting arterial stiffness in the supine position.

Data synthesis

To summarise the effects of exercise training on arterial stiffness, we estimated the weighted mean differences (WMD) of the relative changes (%) with 95% CIs. We used relative changes in our analysis because the RCTs reviewed had used different arterial stiffness measures and units. The relative change in each group was calculated by subtracting the baseline value ($Mean_{pre}$) from the post intervention value ($Mean_{post}$), divided by the baseline value and multiplied by 100% {$Mean_{rc}$ = [($Mean_{post}$–$Mean_{pre}$)/$Mean_{pre}$] ×100%}; Variances were calculated from the standard deviation (SD) of the changes in the intervention and control group. If the SD of the change was not available, the formula $SD_c = \sqrt{[(SD_{pre})^2 + (SD_{post})^2 - 2 \times corr(pre, post) \times SD_{pre} \times SD_{post}]}$ was used for the calculation, for which we assumed a conservative correlation coefficient of 0.5 between the initial and final values (Cornelissen, Fagard, Coeckelberghs, & Vanhees, 2011; Follmann, Elliott, Suh, & Cutler, 1992). Statistical analysis was performed using the software Review Manager (RevMan 5.1; Cochrane Collaboration, Oxford, United Kingdom).

Results

Our literature search revealed 228 potentially relevant records, of which 36 met our inclusion criteria for outcome variables. Excluding 19 trials with non-random allocation to control group, the remaining 17 RCTs were included in the final analysis. Four RCTs consisted of two studies, therefore, 21 studies were separately reviewed (6 aerobic exercises, 11 resistance exercises and 4 combined aerobic plus resistance exercises). A flow chart of studies identified, included and excluded is shown in Figure 1. All studies used parallel group design except for one study using cross-over design. The characteristics and quality assessment of the included RCTs are shown in Table I.

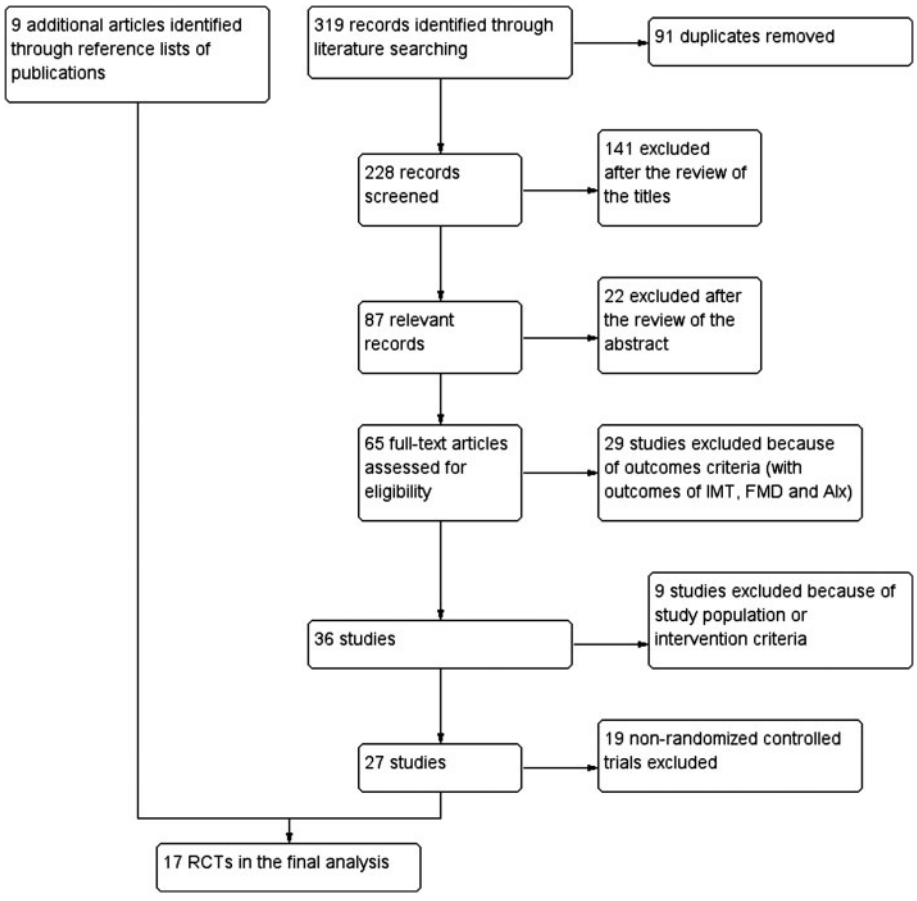

Figure 1. Flow chart of studies identified, included and excluded.

Aerobic exercise and arterial stiffness

Results. We investigated 6 RCTs on the effect of aerobic training on arterial stiffness, involving 8 comparisons and 215 participants. The average age of the participants ranged from 18 to 72 years and 29.3% were male. Training duration varied from 8 to 16 weeks. Training frequency amounted to 2–3 weekly sessions. Training duration per session averaged 30–45 min. Intensity ranged from 50–90% VO_{2max}, 50– 85% HR_{max} or 50–80% HHR. Four of these studies had a Jadad score of ≥3. The combined relative changes in arterial stiffness are reported in Table II.

Two RCTs have measured the changes in arterial stiffness in the context of aerobic training in normotensive young (Ciolac et al., 2010) and middle-aged individuals (Yoshizawa et al., 2009). No RCT was available in the older adults above 60 years old. Combining the data of interval and continuous training, aerobic exercise was associated with a significant reduction in cfPWV by −7.0% (95% CI, −11.3%, −2.6%) in young individuals (Ciolac et al., 2010). Similar result was shown in the middle-aged adults [−6.7% (95% CI, −10.6%, −2.8%)] (Yoshizawa et al., 2009). Comparing the exercise modality of continuous and interval training, the authors showed that vigorous interval training was associated with a significant reduction in cfPWV by −7.5% (95% CI, −13.2%, −1.8%), however, the improvement in arterial stiffness with continuous training was not significant (Ciolac et al., 2010). Regarding the training intensity, combining the data of continuous aerobic exercise (Yoshizawa et al., 2009) and interval aerobic exercise (Ciolac et al., 2010), the vigorous training was associated with a significant improvement in cfPWV by −7.0 (95% CI, −10.2%, −3.8%). However, the improvement of arterial stiffness following moderate continuous aerobic exercise was not significant (Ciolac et al., 2010). All remaining RCTs in this review investigated hypertensive patients with inconsistent results. Three RCTs showed the changes in arterial stiffness in the context of aerobic training in mixed hypertension. In young prehypertensive individuals, peripheral arterial stiffness was significantly reduced [−10.3% (95% CI, −18.4%, −2.2%)] after moderate interval training; however, the central arterial stiffness did not change apparently (Beck, Martin, Casey, & Braith, 2013). In middle-aged hypertensive patients, combining the data of continuous and interval aerobic exercise, vigorous aerobic exercise did not change the central

Table I. Characteristics of the included RCTs: aerobic, resistance and combined exercise training

Study	Design	Participant	Age (years)	Sex	Exercise	Weeks	Frequency/ week	Min/ session	Intensity	N1 (Intervention)	N2 (Control)	Outcome	Mean difference (% change; 95% CI)	Jadad score
Trails including AE														
Yoshizawa et al. (2009)	Parallel	Normotensive	47 ± 2	Female	Cycle ergometer	12	3	30	60–70% VO_{2max}	12	12	cfPWV	−6.74 (−10.64, −2.84)	2
Ciolac et al. (2010)	Parallel	Normotensive females with hypertensive patients	25.0 ± 4.4	Female	Treadmill walking/ running	16	3	40	80–90% VO_{2max} interval training	16	12	cfPWV	−7.5 (−13.21, −1.79)	3
									50–60% VO_{2max} continuous training	16			−6.2 (−12.83, 0.43)	
Beck et al. (2013)	Parallel	Prehypertensive	18–35	Both	Treadmill walking/ running	8	3	45	65–85% HR_{max}	13	15	crPWV	−9.8 (−19.97, 0.37)	3
												cfPWV	−1.00 (−8.52, 6.52)	
												fdPWV	−11.1 (−24.58, 2.38)	
Madden et al. (2009)	Parallel	Hypertension, Hypercholesterolemia	71.4 ± 0.7	Both	Treadmilland cycle ergometer	12	3	40	60–75% HRR	17	17	Radial PWV	−29.2 (−33.54, −24.86)	4
												Femoral PWV	−18.3 (−21.85, −14.75)	
Guimarães et al. (2010)	Parallel	Hypertension	45 ± 9	Both	Treadmill	16	2	40	50–80% HRRinterval training	26	13	cfPWV	−8.6 (−19.35, 2.15)	4
										26			−4.6 (−16.53, 7.33)	
Ferrier et al. (2001)	Cross-over	Isolated systolic hypertension	64 ± 7	Both	Cycle ergometer	8	3	40	65% HR_{max}	10	10	cfPWV	0 (−16.5, 16.5)	1
												fdPWV	2.10 (−16.25, 20.45)	
Trials including RE														
Yasuda et al. (2013)	Parallel	Healthy	61–84	Both	Lower limb	12	2	NG	20–30% 1RM	9	10	CAVI	1.2 (−11.38, 13.78)	1
Okamoto et al. (2008a)	Parallel	Healthy	19.4 ± 0.2	Male	Whole body	8	2	NG	40% 1RM	10	9	baPWV	−6.6 (−13.45, 0.25)	1
Okamoto et al. (2011)	Parallel	healthy	18.5 ± 0.5	Both	Whole body	10	2	NG	50% 1RM	13	13	baPWV	−8.4 (−18.59, 1.79)	3
Kawano et al. (2006)	Parallel	Healthy	20 ± 1	Male	Whole body	16	3	45	50% 1RM	12	16	Carotid arterial compliance	20.0 (7.0, 33.0)	2
												Femoral arterial compliance	−22.5 (−51.38, 6.38)	
Yoshizawa et al. (2009)	Parallel	Healthy	47 ± 2	Female	Whole body	12	2	NG	60% 1RM	11	12	cfPWV	−5.14 (−9.8, −0.48)	2
Beck et al. (2013)	Parallel	Prehypertensive	18–35	Both	Whole body	8	3	45	60% 1RM	15	15	crPWV	−10.5 (−20.20, −0.80)	3
												cfPWV	−2.0 (−9.05, 5.05)	
												fdPWV	−7.9 (−15.26, −0.54)	
Cortez-Cooper et al. (2008)	Parallel	Healthy	52 ± 2	Both	Whole body	13	3	30–45	70% 1RM	13	12	cfPWV	−4.91 (−16.10, 6.28)	2
Okamoto et al. (2006)	Parallel	Healthy	18.9 ± 0.3	Female	Upper limb, eccentric	8	3	NG	100% 1RM	10	9	baPWV	−3.1 (−6.38, 0.18)	3
			19.1 ± 0.3	Female	Upper limb, concentric			NG	80% 1RM	10			10.4 (7.12, 13.68)	
Okamoto et al. (2008b)	Parallel	Healthy	19.6 ± 0.4	Male	Whole body, eccentric	10	2	NG	80% 1RM	10	10	baPWV	−5.55 (−10.37, −0.73)	3
			19.2 ± 0.3	Male	Whole body, concentric			NG		10			8.75 (3.93, 13.57)	
Okamoto et al. (2009)	Parallel	Healthy	20.2 ± 0.4	Both	Upper limb	10	2	NG	80% 1RM	10	10	baPWV	12.18 (5.58, 18.78)	2
			20.0 ± 0.5		Lower limb			NG		10			−1.42 (−8.02, 5.18)	

Table I (*Continued*)

Study	Design	Participant	Age (years)	Sex	Exercise	Weeks	Frequency/ week	Min/ session	Intensity	N1 (Intervention)	N2 (Control)	Outcome	Mean difference (% change; 95% CI)	Jadad score
Miyachi et al. (2004)	Parallel	Healthy	20–38	Male	Whole body	16	3	45	80% 1RM	14	14	Carotid arterial compliance	29.88 (14.17, 45.59)	3
												Femoral arterial compliance	0.00 (−40.34, 40.34)	
Trials including COMB														
Stewart et al. (2005)	Parallel	Mild hypertension	55–75	Both	RE + AE one training session	24	3	RE: NGAE: 45	50% 1RM, 60–90% HR_{max}	40	42	cfPWV	10.5 (−9.08, 30.08)	2
Kawano et al. (2006)	Parallel	Healthy	21 ± 1	Male	RE + AE one training session	16	3	75	80% 1RM, 60% HR_{max}	11	16	Carotid arterial compliance	−12.5 (−26.32, 1.32)	2
												Femoral arterial compliance	12.2 (−15.57, 39.97)	
Cortez-Cooper et al. (2008)	Parallel	Healthy	52 ± 2	Both	RE and AE separate days	13	3	60–90	70% 1RM, 60–75% HR_{max}	12	12	cfPWV	−4.91 (−15.65, 5.83)	2
Figueroa et al. (2011)	Parallel	Healthy	47–68	Female	RE + AE one training session	12	3	40	60% 1RM, 60% HR_{max}	12	12	baPWV	−6.98 (−11.34, −2.62)	1

RE, resistance training; AE, aerobic training; COMB, combined aerobic and resistance training; VO_{2max}, maximal oxygen consumption; HR_{max}, maximal heart rate; HRR, heart rate reserve; NG, not given in the study; 1RM, one repetition maximum; CAVI, cardio-ankle vascular index; baPWV, brachial ankle pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid radial pulse wave velocity; fdPWV, femoral ankle pulse wave velocity; CI, confidence interval; − [Mean difference (% change)], decrease of arterial stiffness or increase of arterial compliance; + [Mean difference (% change)], increase of arterial stiffness or decrease of arterial compliance.

Table II. Combined relative changes in arterial stiffness after aerobic training

	Arterial stiffness	Study	N1 (intervention)	N2 (Control)	Outcome	Combined relative change (%) of arterial stiffness (95% CI)
Normotensive individuals (2 RCTs)						
Intensity						
Moderate	Central	Ciolac et al. (2010)	16	12	cfPWV	−6.2 (−12.8, 0.43)
	Peripheral	No data available				
Vigorous	Central	Yoshizawa et al. (2009) and Ciolac et al. (2010)	28	24	cfPWV	−7.0 (−10.2, −3.8)
	Peripheral	No data available				
Age						
Young (18–39 years)	Central	Ciolac et al. (2010)	32	24	cfPWV	−7.0 (−11.3, −2.6)
	Peripheral	No data available				
Middle-aged (40–59 years)	Central	Yoshizawa et al. (2009)	12	12	cfPWV	−6.7 (−10.6, −2.8)
	Peripheral	No data available				
Old (>60 years)	Central	No data available				
	Peripheral	No data available				
Modality						
Continuous	Central	Ciolac et al. (2010)	16	12	cfPWV	−6.2 (−12.8, 0.4)
	Peripheral	No data available				
Interval	Central	Ciolac et al. (2010)	16	12	cfPWV	−7.5 (−13.2, −1.8)
	Peripheral	No data available				
Mixed hypertension individuals (3 RCTs)						
Intensity						
Moderate	Central	Beck et al. (2013)	13	15	cfPWV	−1.0 (−8.5, 6.5)
	Peripheral	Beck et al. (2013)	26	30	crPWV, fdPWV	−10.3 (−18.4, −2.2)
Vigorous	Central	Guimarães et al. (2010)	52	26	cfPWV	−6.8 (−14.8, 1.2)
	Peripheral	Madden et al. (2009)	34	34	Radial PWV, femoral PWV	−23.7 (−34.4, −13)
Age						
Young (18–39 years)	Central	Beck et al. (2013	13	15	cfPWV	−1.0 (−8.5, 6.5)
	Peripheral	Beck et al. (2013)	26	30	crPWV, fdPWV	−10.3 (−18.4, −2.2)
Middle-aged (40–59 years)	Central	Guimarães et al. (2010)	52	26	cfPWV	−6.8 (−14.8, 1.2)
	Peripheral	No data available				
Old (>60 years)	Central	No data available				
	Peripheral	Madden et al. (2009)	34	34	Radial PWV, femoral PWV	−23.7 (−34.4, −13)
Modality						
Continuous	Central	Guimarães et al. (2010)	26	13	cfPWV	−4.6 (−16.5, 7.3)
	Peripheral	Madden et al. (2009)	34	34	Radial PWV, femoral PWV	−23.7 (−34.4, −13)
Interval	Central	Beck et al. (2013) and Guimarães et al. (2010)	39	28	cfPWV	−3.8 (−11, 3.4)
	Peripheral	Beck et al. (2013)	26	30	crPWV, fdPWV	−10.3 (−18.4, −2.2)
Isolated systolic hypertension individuals (1 RCT)						
	Central	Ferrier et al. (2001)	10	10	cfPWV	0 (−16.5, 16.5)
	Peripheral				fdPWV	2.10 (−16.3, 20.5)

Moderate intensity, 40–59% heart rate reserve = 64–76% maximal heart rate = 46–63% maximal oxygen uptake; Vigorous intensity, 60–89% heart rate reserve = 77–95% maximal heart rate = 64–90% maximal oxygen uptake; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid radial pulse wave velocity; fdPWV, femoral ankle pulse wave velocity; CI, confidence interval; − [Combined relative change of arterial stiffness], decrease of arterial stiffness or increase of arterial compliance; + [Combined relative change of arterial stiffness], increase of arterial stiffness or decrease of arterial compliance.

arterial stiffness significantly (Guimarães et al., 2010). In older hypertensive patients, the vigorous aerobic exercise affected the peripheral arterial stiffness favourably with a combined reduction of radial PWV and femoral PWV by −23.7% (95% CI, −34.4%, −13%) (Madden, Lockhart, Cuff, Potter, & Meneilly, 2009). However, moderate aerobic exercise training did not result in a change of arterial stiffness in patients with isolated systolic hypertension (Ferrier et al., 2001).

Discussion. There is a general agreement that acute aerobic exercise leads to both local (exercising limbs; Kingwell, Berry, Cameron, Jennings, & Dart, 1997) and systemic changes in arterial stiffness (Ranadive et al., 2012). Analogously, for medium to long-term exercise training, similar effects could be speculated.

Our results demonstrate that aerobic exercise training reduced arterial stiffness in healthy normotensive (Ciolac et al., 2010; Yoshizawa et al., 2009) and hypertensive patients (Beck et al., 2013; Guimarães et al., 2010; Madden et al., 2009). However, aerobic exercise failed to alter large arterial stiffness in older populations with isolated systolic hypertension (Ferrier et al., 2001). The central and peripheral arterial stiffness may differ in response to aerobic exercise. In healthy individuals, central arterial stiffness following aerobic exercise decreased significantly (Ciolac et al., 2010; Yoshizawa et al., 2009). In hypertensive patients, aerobic exercise reduced the peripheral arterial stiffness (Beck et al., 2013; Madden et al., 2009); however, the central arterial stiffness did not change significantly (Beck et al., 2013; Guimarães et al., 2010). Since most of the RCTs investigated the association between exercise training and only one arterial stiffness parameter at one segment of the artery, whether the adaptations differ for central and peripheral arterial stiffness in normotensive and hypertensive is largely unknown and should be investigated in future studies. Further, comparing exercise modalities, vigorous interval training was shown to be superior to traditional moderate continuous training in reducing arterial stiffness in normotensive populations at risk for future cardiovascular events (Ciolac et al., 2010). However, whether high intensity interval training is well tolerated in hypertensive patients is unknown. Interval training with a lower intensity (50–80% HRR) caused a small and non-significant improvement in cfPWV, but the difference of cfPWV at baseline level in the interval training group (9.44 ± 0.91 m/s) and control group (10.23 ± 1.82 m/s) leaves a doubt, as to whether the drop in cfPWV (0.41 m/s) following interval training was due to a superior intervention effect compared to the controls (Guimarães et al., 2010). Further, the lower intensity (50–80% HRR) assigned to the hypertensive patients may also contribute to the blunted reduction of arterial stiffness in hypertensive patients (Guimarães et al., 2010). Therefore, further studies are required to confirm that high intensity interval training is superior to traditional moderate continuous training in reducing arterial stiffness in hypertensive patients. Age alone increased arterial stiffness even in the well-trained individuals (Cameron, Rajkumar, Kingwell, Jennings, & Dart, 1999; Tanaka et al., 2000). Furthermore, the increase of arterial stiffness was more pronounced in hypertensive patients (Vaitkevicius et al., 1993; Wallace et al., 2007). Thus, to determine the effect of aerobic exercise in populations whose arterial stiffness has some alteration is of great clinical importance. The previous thought of a point of no return might be changed by the encouraging results in older hypertensive patients (Madden et al., 2009). However, the low responsiveness of patients with isolated systolic hypertension to exercise, which may be due to an irreversible level of arterial stiffness (Tanaka & Safar, 2005), implied that aerobic training initiated at a younger age may be more effective. In addition, since arterial stiffening seems to precede hypertension (Kaess et al., 2012), studies in normotensive individuals with increased arterial stiffness are warranted in order to show a direct preventive effect of aerobic exercise training on the artery. Finally, different muscle contractions in aerobic training may contribute differently on arterial stiffness. It has been shown that aerobic exercise training (running) involves both eccentric (knee extensors) and concentric contractions (ankle plantar flexors) (Bijker, Groot, & Hollander, 2002). However, no study so far has addressed the question of whether concentric and eccentric muscle contractions in aerobic exercise training contribute to different effects on arterial stiffness.

Resistance exercise and arterial stiffness

Results. We identified 11 randomised controlled trials investigating the effect of resistance training on arterial stiffness, involving 14 study groups and 287 participants totally. The average age of the study groups ranged from 18 to 84 years, 56% of the participants were male. Only one trial was conducted in prehypertensive patients (Beck et al., 2013). Training duration varied from 8 to 16 weeks, training frequency averaged 2–3 weekly sessions and intensity ranged from 20–100% of 1RM. Four studies reported the duration per session which averaged 30–45 min (Beck et al., 2013; Cortez-Cooper et al., 2008; Kawano, Tanaka, & Miyachi, 2006; Miyachi et al., 2004). Of these 11 studies, only 5 had a Jadad score of ≥3 (Beck et al., 2013; Miyachi et al., 2004; Okamoto, Masuhara, & Ikuta, 2006, 2008b, 2011). The combined relative changes in arterial stiffness are reported in Table III.

Table III. Combined relative changes in arterial stiffness after resistance training

	Arterial stiffness	Study	N1 (intervention)	N2 (Control)	Outcome	Combined relative change (%) of arterial stiffness (95% CI)
Normotensive individuals (10 RCTs)						
Intensity						
Light	Central	Kawano et al. (2006)	12	16	Carotid arterial compliance	20.0 (7.0, 33.0)
	Peripheral	Kawano et al. (2006)	12	16	Femoral arterial compliance	−22.5 (−51.4, 6.4)
	Systemic	Okamoto et al. (2011), Okamoto et al. (2008a) and Yasuda et al. (2013)	32	32	baPWV, CAVI	−5.7 (−10.9, −0.6)
Moderate	Central	Cortez-Cooper et al. (2008) and Yoshizawa et al. (2009)	24	24	cfPWV	−5.1 (−9.4, −0.8)
	Peripheral	No data available				
	Systemic	No data available				
Vigorous	Central	Miyachi et al. (2004)	14	14	Carotid arterial compliance	29.9 (14.2, 45.6)
	Peripheral	Miyachi et al. (2004)	14	14	Femoral arterial compliance	0 (−40.3, 40.3)
	Systemic	Okamoto et al. (2006), Okamoto et al. (2008b) and Okamoto et al. (2009)	60	58	baPWV	3.1 (1.4, 4.8)
Age						
Young (18 −39 years)	Central	Kawano et al. (2006) and Miyachi et al. (2004)	26	30	Carotid arterial compliance	24.0 (14.0, 34.0)
	Peripheral	Kawano et al. (2006) and Miyachi et al. (2004)	26	30	Femoral arterial compliance	−14.9 (−38.3, 8.6)
	Systemic	Okamoto et al. (2006), Okamoto et al. (2008a), Okamoto et al. (2008b), Okamoto et al. (2009) and Okamoto et al. (2011)	83	80	baPWV	1.1 (−4.5, 6.7)
Middle-aged (40−59 years)	Central	Cortez-Cooper et al. (2008) and Yoshizawa et al. (2009)	24	24	cfPWV	−5.1 (−9.4, −0.8)
	Peripheral	No data available				
	Systemic	No data available				
Old (>60 years)	Systemic	Yasuda et al. (2013)	9	10	CAVI	1.2 (−11.4, 13.8)
Muscle contraction types						
Eccentric	Systemic	Okamoto et al. (2006) and Okamoto et al. (2008b)	20	19	baPWV	−3.9 (−6.6, −1.2)
Concentric		Okamoto et al. (2006) and Okamoto et al. (2008b)	20	19	baPWV	9.9 (7.2, 12.6)
Muscle groups						
Lower limb	Systemic	Okamoto et al. (2009) and Yasuda et al. (2013)	19	20	baPWV, CAVI	−1.0 (−5.7, 3.6)
Upper limb	Systemic	Okamoto et al. (2009)	10	10	baPWV	12.2 (5.6, 18.8)
Prehypertensive patients (1 RCT)						
Intensity	Central	Beck et al. (2013)	15	15	cfPWV	−2 (−9.1, 5.1)
Moderate	Peripheral				crPWV, fdPWV	−8.9 (−14.7, −3)

Intensity "light", <50% 1RM; Intensity "moderate", 50–69% 1RM; Intensity "vigorous", 70–84% 1RM; baPWV, brachial ankle pulse wave velocity; CAVI, cardio-ankle vascular index; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid radial pulse wave velocity; fdPWV, femoral ankle pulse wave velocity; CI, confidence interval; − [Combined relative change of arterial stiffness], decrease of arterial stiffness or increase of arterial compliance; + [Combined relative change of arterial stiffness], increase of arterial stiffness or decrease of arterial compliance.

Light resistance training (≤50%1RM) induced a significant pooled reduction of systemic arterial stiffness measured in baPWV and CAVI of −5.7% (95% CI, −10.9%, −0.6%) in 32 participants in comparison with 32 controls combining 3 studies (Okamoto, Masuhara, & Ikuta, 2008a; Okamoto et al., 2011; Yasuda et al., 2013). However, a relative low intensity of 50% 1RM decreased the carotid arterial compliance by 20% (95% CI, 7.0%, 33%) without changing the femoral arterial compliance (Kawano et al., 2006). Moderate resistance training (>50–70% 1RM) was associated with a reduction of cfPWV by −5.1% (95% CI, −9.4%, −0.8%) in healthy young and middle-age individuals (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009). In contrast, high intensity and concurrent high-volume resistance training was found to have unfavourable effects on arterial stiffness. A training at an intensity of ≥80%1RM, resulted in an increase of central arterial stiffness by 29.9% (95% CI, 14.2%, 45.6%) (Miyachi et al., 2004) and baPWV by 3.1% (95% CI, 1.4%, 4.8%) (Okamoto et al., 2006, 2008b; Okamoto, Masuhara, & Ikuta, 2009) without changing the peripheral arterial stiffness (Miyachi et al., 2004). We further summarised the responses to resistance training in different age groups. In young individuals, resistance training was associated with an increase of central arterial stiffness of 24% (95% CI, 14.0%, 34.0%) (Kawano et al., 2006; Miyachi et al., 2004), but was not associated with changes in peripheral (Kawano et al., 2006; Miyachi et al., 2004) and systemic arterial stiffness (Okamoto et al., 2006, 2008a, 2008b, 2009, 2011). In middle-aged adults, two RCTs showed that resistance training was associated with a reduction of central arterial stiffness by −5.1% (95% CI, −9.4%, −0.8%) (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009). The only existing RCT in older adults showed that light resistance training (20–30% 1RM) with lower limb did not affect the systemic arterial stiffness measured as CAVI (Yasuda et al., 2013). Comparing eccentric and concentric training, eccentric exercise led to a relative change by −3.9% in arterial stiffness (95% CI, −6.6%, −1.2%) and concentric exercise increased arterial stiffness of 9.9% (95% CI, 7.2%, 12.6%) (Okamoto et al., 2006, 2008b). Most of the studies examined dynamic resistance training involving major muscular groups of both the upper and lower limbs. Comparing exercise using upper limb with lower limb, upper limb exercise led to a 12.2% (95% CI, 5.6%, 18.8%) increase of baPWV (Okamoto et al., 2009), while lower limb exercise had not affected the systemic arterial stiffness (baPWV and CAVI)(Okamoto et al., 2009; Yasuda et al., 2013). To our knowledge, the only existing RCT in a small number of prehypertensive patients reported that a 8-week moderate (60% 1RM) whole body resistance training reduced peripheral arterial stiffness (combined crPWV and fdPWV) by −8.9% (95% CI, −14.7%, −3%). However, central arterial stiffness (cfPWV) did not change (Beck et al., 2013).

Discussion. Resistance training has been recommended as an important component in a comprehensive exercise programme by the American College of Sports Medicine in recent years (American College of Sports Medicine, 2009). However, these recommendations were primarily based on its favourable effects on muscular strength (Feigenbaum & Pollock, 1999). Few recommendations with respect to resistance training and cardiovascular function exist so far.

Current evidence suggests that low to moderate intensity resistance training does not result in arterial stiffening measured as carotid-femoral pulse wave velocity (cfPWV) (Cortez-Cooper et al., 2008; Yoshizawa et al., 2009), femoral ankle pulse wave velocity (faPWV) (Yoshizawa et al., 2009) or cardio-ankle vascular index (CAVI) (Yasuda et al., 2013). This is in line with the beneficial blood pressure adaptation to moderate resistance training (Cornelissen et al., 2011). On the other hand, our results show that high intensity and concurrent high-volume resistance training was found to be associated with an increase of arterial stiffness (Miyachi et al., 2004; Okamoto et al., 2006, 2008b, 2009). This is consistent with previous studies reporting blood pressure elevation after vigorous resistance training (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985; Palatini et al., 1989). However, there may be a neutral effect of high intensity resistance training on central arterial stiffness as shown in obese normotensive young men (Croymans et al., 2014). Even a favourable effect on arterial stiffness has been shown for resistance training in a slow eccentric manner (Okamoto et al., 2006, 2008b) or with the lower limbs, although intensity was high (Okamoto et al., 2009). In addition, a non-randomised controlled study showed that progressive high-intensity resistance training without volume increase did not alter arterial stiffness (Casey, Beck, & Braith, 2007). Further, resistance training in young individuals was associated with an increase of central and systemic arterial stiffness, but not peripheral arterial stiffness. However, this was not the case in middle-aged and older adults. One explanation for the divergent effects following eccentric and concentric training could possibly be due to the difference in actively contracting muscle mass, which is lower in eccentric training than concentric training (Komi, Linnamo, Silventoinen, & Sillanpää, 2000; Linnamo, Moritani, Nicol, & Komi, 2003; Madeleine, Bajaj, Søgaard, & Arendt-Nielsen, 2001). The greater amount of active muscle mass in concentric resistance training may cause a stronger

vasopressor response, which again increases the strain on the arteries. Further, compared to eccentric training, concentric training results in a greater increase in blood pressure (Okamoto et al., 2006), which may be associated with a stiffening of the arterial wall (London & Guerin, 1999). The difference in upper limb and lower limb might be explained by higher heart rates (Pivarnik, Grafner, & Elkins, 1988) and higher blood pressure levels (Volianitis & Secher, 2002) induced by upper limb exercises compared to lower limb exercises with the same workload. However, not all RCTs with multiple exercise interventions defined the workloads of eccentric versus concentric exercise or upper versus lower limb exercise to be equivalent for comparison of training effect on arterial stiffness. The results are thus, less convincing. Furthermore, it is of clinical importance to investigate the effects of resistance training on arterial stiffness in hypertension. Noteworthy, the only existing RCT in prehypertensive patients showed that moderate resistance training improved peripheral arterial stiffness (Beck et al., 2013). Further studies are warranted for precise resistance exercise recommendations for hypertensive patients.

Traditional resistance training generally consists of muscular contractions performed at a relatively slow speed. This is different to emerging novel types of resistance training with higher velocity and lower intensity, which may result in differing effects on arterial stiffness. In high-velocity resistance training in which the concentric phase is performed as quickly as possible, force can be produced very fast. This aspect of power production is important in activities of daily living, especially with respect to fall prevention (Orr et al., 2006; Sayers & Gibson, 2014). It has been shown that high-velocity resistance training causes a greater increase in muscle power than low-velocity resistance training (Fielding et al., 2002). However, no study exists on the effect of high-velocity resistance training on arterial stiffness. Compared to lower velocity, higher velocity resistance movements with a quick concentric phase might have a smaller impact on arterial stiffness because of a smaller vasopressor response. In view of an ageing population with an increasing prevalence of hypertension (Kearney et al., 2005), and the progressive reduction in muscular power (Reid & Fielding, 2012) and strength (Doherty, 2003), there is an urgent clinical need to define the optimal type of resistance exercise training. The ideal resistance training should provide muscular benefits without health hazards to the vasculature. At best, the individualised resistance training programme has a destiffening effect on the arteries.

Combined aerobic/resistance exercise and arterial stiffness

We included four RCTs on the effect of combined aerobic and resistance exercise training on arterial stiffness in our analysis. These trials involved 8 study groups and 157 participants. Within the 4 studies, the average age of the study groups ranged from 20 to 75 years and 31% of the participants were male. Only one trial was conducted in patients with untreated milder forms of hypertension (Stewart et al., 2005). Training durations varied from 12 to 24 weeks, training frequency amounted to 3 weekly sessions, the training intensity ranged from 50–80% of 1RM and 60–90% HR_{max} and training duration per session averaged 40–90 min.

The resistance exercises were either directly followed by the aerobic exercise within one training session (Figueroa, Park, Seo, Sanchez-Gonzalez, & Baek, 2011; Kawano et al., 2006; Stewart et al., 2005) or on alternating days (Cortez-Cooper et al., 2008). Combined training either had a small or no positive effect on arterial stiffness, suggesting that combined exercise may be of particular relevance for the prevention of sarcopenia in elderly population without arterial stiffening. Aerobic following resistance training in the same exercise session may favourably affect arterial stiffness, but could decrease the gain in muscular strength (Kawano et al., 2006; Sale, Jacobs, MacDougall, & Garner, 1990). The mammalian target of the rapamycin complex 1 (mTORC1), known as a protein complex that controls protein synthesis, and thus, is important for regulating muscle mass, was induced by resistance training and can be down-regulated by aerobic training (Ogasawara, Sato, Matsutani, Nakazato, & Fujita, 2014). Therefore, in order to minimise the attenuation of strength gain, resistance and aerobic training should preferably be performed on alternating days (Kawano et al., 2006; Sale et al., 1990). However, the portion, intensity and sequence of the aerobic and resistance exercise components in the combined exercise programme may all contribute to the discrepancy of the results. Another aspect worth consideration is the good health status in the studies included in our analysis, whereby the results cannot be generalised to other populations. Furthermore, none of the 4 studies included had a Jadad score of ≥3, and thus, all were of lower study quality. Thus, there is an evident need for additional studies on the effect of combined aerobic and resistance training on arterial stiffness in normotensive and hypertensive individuals.

Limitations

There are some limitations that have to be considered. First, we included only the RCTs using the

regional and local arterial stiffness parameters mentioned above. The estimates in this study should be interpreted with caution when compared to other arterial stiffness parameters. Second, we only evaluated studies which reported precise data of change in arterial stiffness in both intervention and control group. Therefore, the estimates were synthesised from the limited data in studies published in English language, and we cannot fully exclude publication bias. Furthermore, the poor methodological quality of some included trials should be acknowledged. We assessed the quality of the included studies using Jadad scale, but we have not excluded the RCTs with a Jadad score <3. We reported all the RCTs that we found according to our inclusion criteria. The existing evidence does not allow firm conclusions. The interpretation is hampered by the use of different measures of arterial stiffness, varying exercise programmes (modality, duration, intensity and frequency), different population-based variables (age, health status) and several confounding factors (e.g. exercise induced weight loss, daily physical activity, diet, medication).

Conclusions

The available evidence indicates that aerobic exercise training is more likely to have a beneficial effect on arterial stiffness in normotensive and hypertensive patients, but does not affect arterial stiffness in patients with isolated hypertension. Resistance exercise seems to have no adverse effect on arterial stiffness if the training is of low intensity, in a slow eccentric manner or with lower limb in healthy individuals. However, intensive concentric resistance exercise increases arterial stiffness in healthy individuals, and thus, should be avoided in populations with an increased cardiovascular risk. Combined training with resistance training first, followed by endurance training, has neutral or even beneficial effects on arterial stiffness based on limited number of studies available.

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Appendix B

Publication: Feasibility of Aortic Pressure and Stiffness

This manuscript has been published in the journal Blood Pressure Monitoring. The final publication is available at http://journals.lww.com/bpmonitoring/Abstract/publishahead/Feasibility_of_oscillometric_aortic_pressure_and.99671.aspx

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Feasibility of oscillometric aortic pressure and stiffness assessment using the VaSera VS-1500: comparison with a common tonometric method

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Objectives **A number of operator-independent oscillometric devices to measure hemodynamics and arterial stiffness became available recently, but some and in particular VaSera VS-1500 do not provide estimates of aortic pressures and aortic pulse wave velocity (aPWV). The aim of this work was the retrospective application of the ARCSolver algorithm to pulse wave signals acquired with the VaSera VS-1500 device to estimate central systolic blood pressure (cSBP) and aPWV.**

Materials and methods **ARCSolver estimates of cSBP and aPWV, on the basis of brachial cuff measurements, were compared pair-wise with results from the tonometric SphygmoCor device in 68 individuals (mean age 51 ± 18 years). We used variation estimates, correlation coefficients, age group-related *t*-tests, and the Bland–Altman method to analyze the reproducibility and agreement of the two methods.**

Results **cSBP reproducibility expressed as variability was 14.9% for ARCSolver and 11.6% for SphygmoCor. PWV reproducibility was better for ARCSolver, with a variation estimate of 6.5%, compared with 20.9% using SphygmoCor. The mean cSBP difference was 0.5 mmHg (SD 6.9 mmHg) and 0.32 m/s (SD 1.20 m/s) for PWV, respectively. The age-related differences between ARCSolver and SphygmoCor are in line with previous studies. Bland–Altman plots showed considerable agreement between the two methods without signs of systematic bias.**

Conclusion **These results show that the combined application of the ARCSolver method with the VaSera VS-1500 device is feasible and the results are comparable with tonometric determination of cSBP and aPWV. This successful application of the ARCSolver may potentially help to improve cardiovascular risk stratification and prevention at an early stage in a community setting. *Blood Press Monit* 20:273–279**

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Keywords: aortic stiffness, ARCSolver, central blood pressure, oscillometry, pulse wave velocity, SphygmoCor, tonometry, VaSera

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Introduction

Aortic hemodynamics and arterial stiffness are considered to be important determinants of improved cardiovascular risk stratification [1,2]. To date, the usability of available devices seemed to be a drawback for the routine use of arterial stiffness surrogates. However, a number of cuff-based operator-independent devices from various manufacturers became available recently [3,4] featuring central hemodynamics and pulse wave velocity (PWV). Furthermore, specific algorithms [5–7] used to estimate arterial stiffness surrogates have been shown to be applicable to measurement signals derived from different devices [8].

Beyond traditional indices of arterial stiffness, new parameters, such as brachial to ankle pulse wave velocity [9] or the cardio-ankle vascular index (CAVI) [10], have emerged within the last few years. These methods typically use two to four cuffs applied to the extremities, which promise simple and unbiased data assessment. However, such solutions do not provide estimates of aortic pressures and aPWV. Therefore, the aim of this work was the retrospective application of algorithms estimating arterial stiffness surrogates to pulse wave signals acquired with the VaSera VS-1500 device and a pair-wise comparison with tonometrically acquired measures of arterial stiffness.

Materials and methods

Study population

We included 68 of a total of 75 individuals in these analyses with valid measures of PWV and pulse wave analysis (PWA), who were participating in an arterial stiffness diurnal variation study described previously [11]. Two individuals dropped out and five had to be

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Table 1 Baseline characteristics

Men/women [*n* (%)]	30 (44)/38 (56)
Hypertensive cardiomyopathy	9
Previous myocardial infarction	13
Previous stroke	2
Compensated heart failure	1
Age (years)	51 (18)
Height (cm)	170.7 (8.9)
Weight (kg)	68.8 (14.9)
SBP (mmHg)	115.1 (12.6)
DBP (mmHg)	96.3 (8.3)
Heart rate/min	58.1 (9.0)

Values are either absolute numbers, percentage, or mean (SD).
DBP, diastolic blood pressure; SBP, systolic blood pressure.

excluded because of insufficient measurement quality: one VaSera measurement with more than one unit difference between the two consecutive measurements, three SphygmoCor measurements with SDs higher than 10%, and one ARCSolver PWA because of insufficient recording quality. Recruitment resulted from poster advertisement in our outpatient clinic. Inclusion criteria were age between 18 and 80 years and being either healthy or having a medical history of coronary heart disease, hypertension, or previous stroke. Acute illness or acute infections were the exclusion criteria. Twenty-five individuals had heart disease under clinically stable conditions without clinical signs of peripheral arterial occlusive disease (Table 1). According to medical history, physical examination, and resting ECG, 50 participants did not have cardiovascular disease and diabetes. The Ethics Committee of the University of Basel granted ethical approval for this study. Participants provided written informed consent to participate in the study.

Method of investigation

Arterial stiffness was measured using two devices: the SphygmoCor (AtCor Medical Pty Ltd, West Ryde, New South Wales, Australia) and a VaSera VS-1500 vascular screening system (Fukuda Denshi Co. Ltd, Tokyo, Japan) applying the ARCSolver algorithm retrospectively [7]. Measurements were performed at 09:00, 13:00, and 17:00 h within 1 day. For the present analyses, the data at 13:00 h were taken. All measurements were performed following a standardized protocol by one observer in a quiet room with a temperature of 22–24°C and complied with international recommendations [12]. After resting for at least 10 min, two to three measurements were obtained with each device (VaSera and SphygmoCor) at 5 min intervals in a supine position. The order of the measurements was randomized. The measurements were obtained under fasting conditions with the participants being asked to refrain from caffeine intake, alcohol intake, smoking, and exercise for at least 12 h.

SphygmoCor measurements

The carotid-femoral pulse wave velocity (cfPWV) was measured using the SphygmoCor device. Pulse waves were recorded using a single high-fidelity applanation tonometer (Millar Instruments, Houston, Texas, USA) at the right carotid artery and the right femoral artery. ECG was used to synchronize the carotid and femoral pulse wave times and to derive the transit time using a foot-to-foot method with an intersecting tangent algorithm. The transit distance was measured superficially with a tape measure by subtracting the distance from the carotid measuring site to the suprasternal notch from the distance between the suprasternal notch and the femoral measuring site [13]. cfPWV was calculated by dividing the time delay of the pulse wave between the two measuring sites by the transit distance (in meters per second). Two consecutive cfPWV measurements had to be within 1.5 m/s with an SD of less than 10% to be included in the analyses [14]. For pulse wave calibration, blood pressure (BP) was measured at the right upper arm using an Omron M9 Premium device (Omron Healthcare, Kyoto, Japan). Furthermore, the SphygmoCor software allows the calculation of central hemodynamic parameters from pulse waves measured at the carotid artery using a generalized transfer function. In contrast to recordings taken at the radial artery, the transfer function applied for recordings from the carotid artery uses a different calibration method, as described in the 'SphygmoCor Research Applications Manual'. The central systolic blood pressure (cSBP) was estimated using this procedure by calibrating the aortic pulse wave, derived by the generalized transfer function, with the brachial diastolic and mean pressure. The mean pressure was calculated by adding the brachial diastolic pressure and 0.4 times the brachial pulse pressure measured by the Omron device [15,16]. In accordance with the 'SphygmoCor Research Applications Manual', the calibration was modified to diastolic and mean pressure and a PWA was created using the carotid pressure waveform and the carotid transfer function.

VaSera measurements

The VaSera device is commonly used to assess arterial stiffness by means of the CAVI. CAVI is based on the oscillometric measurement of the PWV from the heart to the ankle [10]. We, however, used the VaSera device to apply the ARCSolver method to derive central hemodynamic estimates on the basis of peripheral pulse waves, recorded at the brachial artery. Common BP cuffs were placed above each ankle and at each upper arm. The cuffs were kept at 30–50 mmHg to reduce the effect of cuff pressure. ECG leads were attached at each wrist and a phonocardiogram on the sternal border in the second intercostal space. On the basis of the peripheral recordings, PWA was performed using the ARCSolver to derive aPWV and cSBP. CAVI measurements were considered to have acceptable quality when the difference between the two measurements was less than 1 U.

ARCSolver

The ARCSolver method (AIT Austrian Institute of Technology GmbH, Vienna, Austria) is a mathematical

procedure for the calculation of central aortic hemodynamic measures, for example aPWV and cSBP, from peripheral pulse waves and BP measurements at the brachial artery using a common occlusive cuff [5]. In its original configuration, the measurement starts with a conventional oscillometric BP measurement, followed by a 10 s continuous recording with a constant cuff pressure at the diastolic BP level using conventional BP cuffs [17]. As described by Wassertheurer *et al.* [7], these recordings are digitized and a multistep processing algorithm is applied. The first step consists of the separation of the continuous measurement into single pressure waves and the verification of their plausibility by testing the position of their minima and corresponding wavelengths. During the second stage, artifacts are detected by comparing all pressure waves with each other. Aortic pulse waves are calculated by a general transfer function on the basis of the modification of a certain frequency range in the recorded peripheral pressure waves. In the third step, the coherence of the measured parameters is verified by comparing the inflection point of each pulse wave with their average inflection point. Finally, on the basis of these calculations, the central hemodynamic parameters cSBP, aPWV, and others are estimated.

ARCSolver for VaSera measurements

As stated above, the VaSera device performs continuous cuff measurements of pulse waves on several sites of the human body. The ARCSolver is capable of calculating central hemodynamic values using peripheral pulse wave measurements. Therefore, these two systems can be combined easily using the VaSera device for data acquisition and the ARCSolver method for parameter estimation. Only small adaptations had to be made to compensate for the differences in sampling frequency (100 Hz for ARCSolver, 1000 Hz for VaSera) and sampling duration (10 s for ARCSolver, 5 s for VaSera). Therefore, the measured signal was downsampled and doubled in duration when transferred from VaSera to ARCSolver. The VaSera device provides measurements from four sites of the body: left and right ankle and left and right upper arm. As the ARCSolver needs recordings from the brachial artery, the measurements at the ankle were not taken into further consideration. For this work, the pulse waves at the left upper arm were chosen for evaluation by the ARCSolver as this is the common location for oscillometric PWA [18]. However, for reasons of comparability and compatibility, these pulse waves were calibrated using the same diastolic and mean BP values as used for the SphygmoCor device, that is measured at the right upper arm by an Omron device.

Statistics

If not stated otherwise, data are expressed as mean (SD) and are normally distributed. We used the Bland–Altman method to analyze the agreement between the two methods and for graphical representation [19]. Pearson's linear correlation coefficient was calculated for correlation analyses. *T*-tests were applied for examination of age group-related differences between the measurements. Furthermore, box plots were used to visualize the distribution of the values grouped by age and measurement methods.

Reproducibility of the methods was quantified as variation estimate, as described by Bland and Altman [19]. It is calculated by using twice the SD of the differences between two consecutive measurements at the same time point and the same participant, and presented as percentage of the overall average of all measurements in all participants [19]. The scientific computing environment MATLAB 7.5 (The Mathworks Inc., Natick, Massachusetts, USA) was used for statistical analyses. A *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical parameters of the cohort

We analyzed measurements of 68 individuals in this study, 38 women and 30 men. The mean age of the participants was 51 years, with an SD of 18 years, ranging from 21 to 79 years. The mean systolic BP was 115.1 mmHg (SD 12.6 mmHg) and the mean diastolic BP was 69.3 mmHg (SD 8.3 mmHg). Further baseline values are listed in Table 1. A sensitivity analysis showed no difference in the results when analyzing data from a different time point than 13:00 h (data not shown).

Reproducibility of measurements

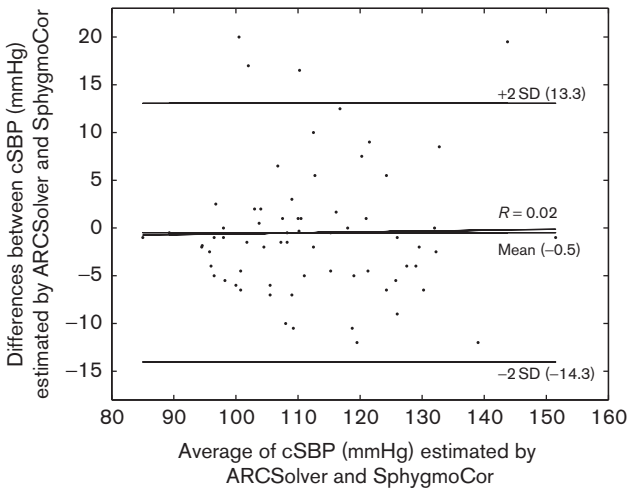
The variation estimate as a measure of reproducibility of the cSBP readings resulted in 11.6% for the SphygmoCor method and 14.9% for ARCSolver. For the cfPWV measured using SphygmoCor, the reproducibility was 20.9% and for the aPWV calculated by the ARCSolver, the reproducibility was 6.5%. The mean SD of consecutive measurements of the cSBP was 3.8 mmHg (SD 3.2 mmHg) for SphygmoCor and 3.6 mmHg (SD 4.2 mmHg) for ARCSolver. For the cfPWV measured using SphygmoCor, the mean SD was 0.40 m/s (SD 0.39 m/s) and for the aPWV calculated by the ARCSolver the mean SD was 0.11 m/s (SD 0.12 m/s).

Comparison of cSBP

The mean cSBP results were 112.5 mmHg (SD 13.8 mmHg) for SphygmoCor and 112.0 mmHg (SD 13.9 mmHg) for ARCSolver. The mean differences were 0.5 mmHg (SD 6.9 mmHg). The results correlated strongly, showing a Pearson's linear correlation coefficient of $R = 0.88$ ($P < 0.001$). Bland–Altman plots in Fig. 1 show the per-subject differences, with a very low Pearson *R* coefficient of 0.02 between differences and means [20].

Furthermore, the cohort was divided into six age groups with 10-year intervals (Fig. 2). The differences in the two methods did not show any relation to age, whereas the

Fig. 1



Bland–Altman analysis of central systolic blood pressure (cSBP) as calculated by SphygmoCor versus VaSera & ARCSolver.

absolute values and their spread increased with age for both calculation methods. The difference in the age group 70–79 years was found to be significant ($P < 0.05$), whereas the differences in all the other age groups were not significant.

Comparison of PWV

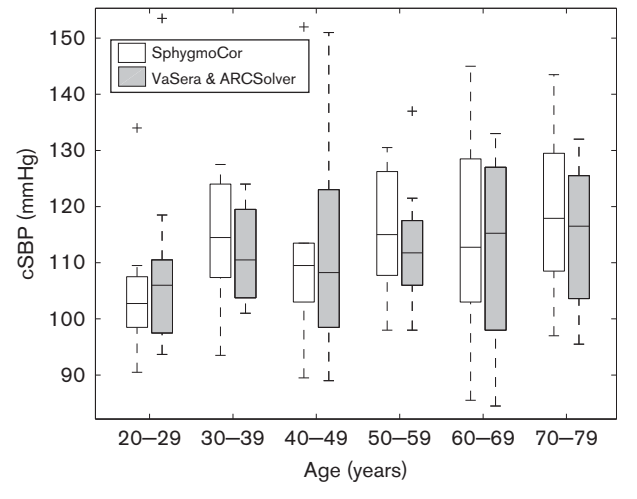
Similar to cSBP, PWV was acquired with the ARCSolver using measurements from VaSera and were compared with measurements of cfPWV acquired with the SphygmoCor device. Again, at least two consecutive recordings were evaluated for each instant. The mean results were 7.25 m/s (SD 1.66 m/s) for SphygmoCor and 7.57 m/s (SD 2.25 m/s) for ARCSolver. The mean difference was 0.32 m/s (SD 1.20 m/s). Pearson's linear correlation coefficient for these results was $R = 0.85$ ($P < 0.001$). Figure 3 shows the Bland–Altman analysis of these differences, with a Pearson R coefficient of 0.51 between differences and means [20].

Again, we investigated the results of the PWV grouped by age. The results are presented in Fig. 4 and show a strong correlation with age. The difference between the two methods varied with age, with a tendency toward higher values for the VaSera and ARCSolver method in participants older than 50 years of age. For younger participants, the PWV readings from SphygmoCor were higher than those of VaSera and ARCSolver. Furthermore, these differences were found to be significant ($P < 0.05$) for the age groups 20–29, 30–39, 60–69, and 70–79 years, as listed in Table 2.

Discussion

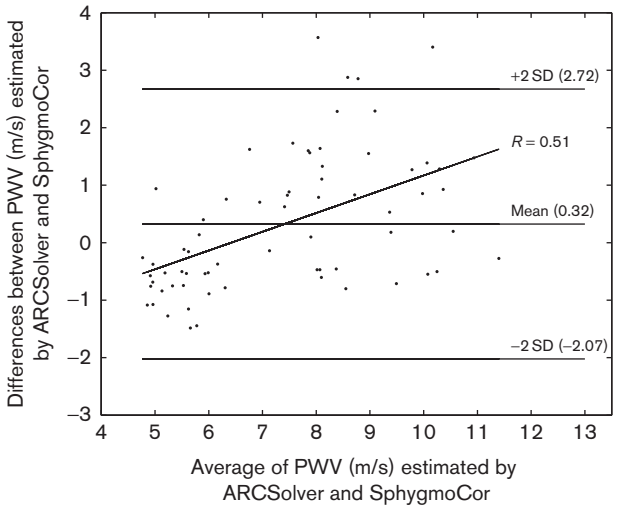
Our study shows considerable agreement of oscillometrically measured cSBP and acceptable agreement of aPWV by the ARCSolver method, combined with a VaSera VS-1500 vascular screening system, with the noninvasive gold-standard tonometric SphygmoCor device. Central SBP varies extensively from brachial SBP and also within one individual at all age groups [21]. In recent years, growing evidence has suggested that central BP may be a better predictor of cardiovascular risk compared with brachial BP, and may reduce hypertension misclassification [22]. However, measurement of central BP with a tonometer relies very much on the skills and training of the operator and is rather unsuitable for large-scale assessments [21]. The assessment of central pressure and wave reflection by the ARCSolver algorithm has been

Fig. 2



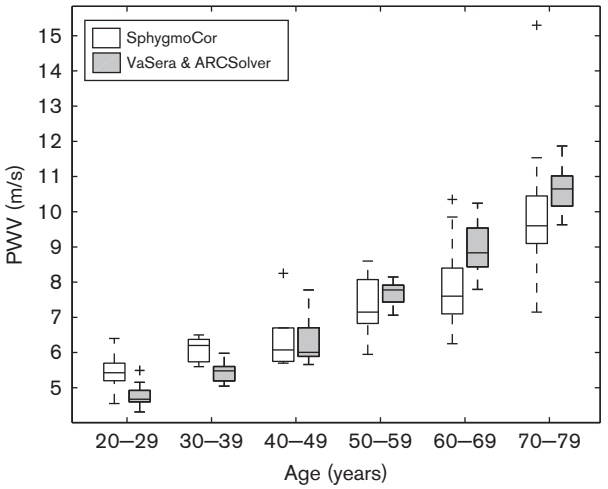
Distribution of central systolic blood pressure (cSBP) by age and method. Box represents 25th percentile (lower edge), median (middle bar), and 75th percentile (upper edge). Whiskers show the extent of the rest of the data; + indicates outliers.

Fig. 3



Bland–Altman analysis of pulse wave velocity as measured by SphygmoCor (cfPWV) versus acquired with VaSera & ARCSolver (aPWV). PWV, pulse wave velocity.

Fig. 4



Distribution of pulse wave velocity (PWV) by age and method. Box represents 25th percentile (lower edge), median (middle bar), and 75th percentile (upper edge). Whiskers show the extent of the rest of the data; + indicates outliers. PWV, pulse wave velocity.

Table 2 Mean (SD) values for path length and delta *t* for SphygmoCor measurements, comparison of PWV, and differences by age groups

Age group (years)	*N*	Mean (SD) path length SphygmoCor (mm)	Mean (SD) delta *t* SphygmoCor (ms)	Mean (SD) cfPWV SphygmoCor (m/s)	Mean (SD) aPWV VaSera and ARCSolver (m/s)	Mean (SD) difference (m/s)	*P*-value
20–29	15	421 (28)	76 (6.8)	5.44 (0.45)	4.76 (0.31)	−0.68 (0.57)	0.0001
30–39	8	450 (31)	73 (5.1)	6.07 (0.35)	5.44 (0.31)	−0.63 (0.45)	0.0028
40–49	6	447 (25)	69 (9.4)	6.43 (0.97)	6.34 (0.79)	−0.08 (0.61)	0.7499
50–59	8	465 (24)	64 (8.7)	7.33 (0.88)	7.68 (0.36)	0.35 (0.72)	0.2122
60–69	18	453 (27)	58 (7.3)	7.92 (1.11)	8.96 (0.70)	1.04 (1.18)	0.0017
70–79	13	443 (31)	46 (6.5)	9.41 (1.23)	10.67 (0.70)	1.25 (1.20)	0.0027

aPWV, aortic pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; PWV, pulse wave velocity.

validated invasively and noninvasively [3,18,23]. It has also been shown that it is a reproducible and feasible method in a laboratory [7,18,24] and community setting [17]. The aPWV estimation of the ARCSolver has been proven to have very good accuracy both in noninvasive [18] and in invasive comparisons [25]. The ARCSolver aPWV method is also applicable and robust in large-scale, community-based studies [26]. We can now successfully apply the ARCSolver algorithm to a different oscillometric arterial stiffness measurement device.

The reproducibility of measurement is influenced by several factors. It depends on the physiologic variability of the parameters, the effect of the investigator, and the stability of the measurement method. As the minimization of the physiologic variability is addressed by study protocols ensuring constant and equal conditions for each measurement, the remaining variability can be attributed to the operability and stability of the methods. In our study, the short-term, within-session reproducibility of the cSBP and aPWV measurement is high and very acceptable for clinical practice with a low SD of the differences [27–29] and low variation estimates [7,18]. This result is also in line with the previously shown low day-to-day variation in the same study population of the parameters CAVI and cfPWV [11]. Furthermore, the results are similar for both devices, with a considerably lower variation estimate for the ARCSolver compared with SphygmoCor. This shows that the ARCSolver method combined with a VaSera device is comparable in terms of reproducibility to a commonly used tonometric measurement.

The SD as a measure of variability of the cSBP mean difference (6.9 mmHg) is similar to previous studies comparing the ARCSolver method in noninvasive and invasive settings [3,7,23,30]. This SD and the mean difference of 0.5 mmHg are well below the threshold of ±5 (8 SD) mmHg recommended by the Association for the Advancement of Medical Instrumentation [27]. Even though the mean difference is very low, it may partly have resulted from different measuring sites as SphygmoCor measures at the carotid artery, but the ARCSolver estimation refers to central BP on the basis of brachial measurements. Furthermore, the carotid transfer function implemented in the SphygmoCor software has not been approved for clinical use in the USA, as described in the 'SphygmoCor Research Applications Manual', which can be considered a limitation to our study. The Bland–Altman plot, however, shows no sign

of a homogenous scattering pattern toward the mean or difference of both methods, which reflects good agreement.

The mean difference between the ARCSolver aPWV and cfPWV of SphygmoCor of 0.32 m/s (SD 1.20 m/s) is very consistent with previous comparisons, both invasive [25,31] and noninvasive [18]. The mean difference can be considered as excellent and the SD as acceptable according to the ARTERY Society validation guidelines [20]. Accordingly, the Bland–Altman plot shows very good agreement as there is no sign of systematic bias between the two methods. The Pearson *R* coefficient of 0.51 in the Bland–Altman plot can be attributed to the age-related cross-over effect described below.

The age group analyses show that cfPWV and aPWV measured with the SphygmoCor and ARCSolver, respectively, reflect the expected age-dependent increase. We also observed a slight exponential increase in aPWV with increasing age as found with both MRI and tonometrically measured aPWV [32] and in a community setting [26]. This is a crucial feature of the method as age is the main determinant of vascular modification besides BP [1,33]. In contrast to our cSBP results, the PWV difference between the two methods is inconsistent over the age range. The observed cross-over effect of the PWV difference at the middle age is in line with previous findings; tonometrically measured cfPWV has been shown to overestimate aortic stiffness in younger individuals and to underestimate this in older individuals compared with direct invasive assessment [31,34]. This effect is because of the increasing cfPWV travel distance with age, especially within the aortic arch [32, 34], and the significant decrease in the difference in travel time between aPWV and cfPWV [34,35]. This also explains the systematic, and for four age groups, significant difference between the two methods. Nevertheless, tonometric cfPWV and aPWV measured invasively and using MRI have shown good agreement [31,32]. Comparably, the ARCSolver aPWV correlated well with invasively measured aPWV [31].

Conclusion

These study results establish considerable agreement between cSBP and acceptable agreement between aPWV measured with the ARCSolver method combined with an oscillometric PWA device and the tonometric SphygmoCor device. This suggests that the ARCSolver algorithm can be applied successfully to other devices to estimate aortic stiffness and aortic hemodynamics, which may improve cardiovascular risk assessment and prevention at an early stage. Moreover, further studies can also benefit from the ARCSolver's capabilities to carry out wave separation analysis and the determination of other central hemodynamics parameters.

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Conflicts of interest

S.W. and C.M. are the inventors (not holder) of a patent that is partly used in the ARCSolver algorithm. For the remaining authors there are no conflicts of interest.

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