Associations Between Cardiorespiratory Fitness and Arterial Stiffness in Ankylosing Spondylitis: A Cross-sectional Study

Berg, I.J.; Semb, A.G.; Sveaas, S.H.; Fongen, C.; Heijde, D. van der; Kvien, T.K.; ... ; Provan, S.A.

Associations between cardiorespiratory fitness and arterial stiffness in ankylosing spondylitis; a cross-sectional study

Inger Jorid Berg, Anne Grete Semb, Silje H Sveaas, Camilla Fongen, Désirée van der Heijde, Tore K Kvien, Hanne Dagfinrud, Sella A Provan

Key Indexing Terms: ankylosing spondylitis, cardiorespiratory fitness, arterial stiffness

The work should be attributed to Department of Rheumatology, Diakonhjemmet Hospital.

The work was supported by The Norwegian Rheumatism Association

I. J. Berg, MD, PhD; S. H. Sveaas, PhD; C Fongen MSc; T. K. Kvien, MD, PhD; H Dagfinrud, PhD; S. A. Provan, MD, PhD, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; A. G. Semb, MD, PhD; Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; D. van der Heijde, MD, PhD, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway and Department of Rheumatology, Leiden University Medical Center, Leiden

Corresponding author: Inger Jorid Berg, Diakonhjemmet Hospital, Box 23 Vinderen, N-0319 Oslo, Norway; telephone number +47 22451500; E-mail: ingerjoridberg@gmail.com

Running head: AS, cardiorespiratory fitness, arterial stiffness

Word count: Abstract: 100; Main document: 1600

Abstract

Objective: To assess associations between cardiorespiratory fitness (CRF), measured as peak oxygen uptake (VO_2peak) and cardiovascular disease (CVD) risk, measured by arterial stiffness, in patients with ankylosing spondylitis (AS).

Methods: VO_2peak was assessed by a maximal walking test on treadmill. Arterial stiffness was measured non-invasively (Sphygmocor apparatus). Cross-sectional associations between VO_2peak and arterial stiffness were analysed using backwards multivariable linear regression.

Results: Among 118 participating patients there were significant inverse associations between VO_2peak and arterial stiffness independent of traditional CVD risk factors and measures of disease activity.

Conclusion: Reduced CRF may be related to increased risk of CVD in AS.

Introduction

Physical activity is a cornerstone of the treatment of ankylosing spondylitis (AS), and traditionally the focus has been on flexibility exercises. The majority of the AS patients reports to perform low intensity exercises (1;2), which does not improve cardiorespiratory fitness (CRF), and a study found that AS patients have lower CRF than controls (3).

CRF is the circulatory and respiratory systems ability to supply oxygen to the skeletal muscles during sustained physical activity, and the most important lifestyle factor to improve CRF is physical activity at moderate to high intensity (4). CRF can be measured as maximum oxygen uptake (VO_2peak) with gas-analyses during maximum exercise or estimated by indirect exercise-tests calculating VO_2peak (3-5). Low CRF is an independent predictor of cardiovascular disease (CVD) in the general population and in patient groups with increased risk of CVD such as diabetes (6), and improvement of CRF is associated with lower risk of CVD (4). Possibly, also in patients with AS, low CRF is a risk factor of CVD, however this has not been analysed previously.

Patients with AS have an increased risk of CVD (7), and arterial stiffness, a validated marker of CVD risk (8), has been shown to be elevated in AS patients (9;10). In the general population, there is an inverse association between CRF and arterial stiffness (11;12). The hypothesis of this study was that there is an inverse relationship between CRF and arterial stiffness independent of traditional CVD risk factors and disease activity in AS patients.

Methods

This was a cross-sectional study in a cohort of patients with AS described previously (10). The study was approved by the local Committee of Ethics (approval number S-02059) and performed according to the Helsinki declaration. All patients gave their written consent.

Information on demographics, height at adulthood, medical history and medications was self-reported in questionnaires, and later confirmed in an interview with a cardiologist. Body mass index (BMI) was calculated from measured height and weight. Loss of height was calculated as height at adulthood minus height at data collection. C-reactive protein (CRP), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-c) were analysed consecutively. Disease activity was assessed by the AS Disease Activity Score (ASDAS)-CRP and by Bath AS Disease Activity Index (BASDAI) (13;14).

CRF was estimated indirectly as VO_2peak by a maximal walking test on a treadmill (modified Balke protocol) described previously (Supplementary file 1) (3). The test was ended when the participants were unable to increase inclination or speed of the treadmill and reported a perceived exertion on Borgs scale 17-20 (3).

Brachial blood pressure (BP) and arterial stiffness were measured after at least 5 minutes of supine rest. Arterial stiffness was measured non-invasively (Sphygmocor apparatus) both as Augmentation Index (AIx) and Pulse Wave Velocity (PWV), described in detail previously (Supplementary file 1) (10).

The statistical analyses were performed using SPSS version 21. Unadjusted associations between VO_2peak and arterial stiffness were investigated in scatterplots with calculation of regression-lines.

AIx and PWV were dependent variables in separate age and gender adjusted univariate linear regression analyses. We included the following independent variables: VO_2peak, traditional CVD risk factors (smoking, BMI, TC, HDL-c and central mean arterial pressure), measures of inflammation and disease activity (CRP and ASDAS), use of non-steroidal anti-inflammatory drugs and other factors known to influence the arterial stiffness measurements (height in AIx analyses and loss of height in PWV analyses). PWV was log transformed to obtain normality of the residuals.

We then performed backwards mulitivariable regression with variables with a p-value<0.25. Non-significant variables (p-value≥0.05) were removed until only significant variables (p-value<0.05) remained. Non-significant variables from the adjusted univariate analyses were re-entered into the

final model to check for confounding. We assessed possible interactions between CRP and VO_2peak as well as ASDAS and VO_2peak. The residuals of the final models were assessed for normality. We also performed similar analyses excluding patients with established CVD.

Results

Out of 159 AS patients in the cohort, 118 patients had available data on both CRF and arterial stiffness. Missing data were mostly due to logistic reasons (Supplementary figure S1). Descriptive data are given in Table 1.

Scatterplots (Figure 1) indicated inverse relations between VO_2peak and both AIx ($p<0.001$) and PWV ($p<0.001$). In the multivariable linear regression models, VO_2peak was independently and inversely associated with AIx (beta (95% confidence interval)) -0.3 (-0.6, -0.1), p=0.01 and lnPWV (-0.005 (-0.010, -0.001)), p=0.03 (Table 2). There were no interactions between CRP and VO_2peak or ASDAS and VO_2peak. Analyses with exclusion of patients with established CVD (9 patients) did not alter results (data not shown).

Discussion

Our data demonstrate cross-sectional independent inverse associations between VO_2peak (a measure of CRF) and arterial stiffness (a measure of CVD risk), assessed both as AIx and PWV in patients with AS.

Although similar inverse relations between CRF and arterial stiffness have been found in the general population (11;12), we have not identified other studies analysing associations between CRF and arterial stiffness in patients with AS or other inflammatory joint diseases (IJD). In patients with

rheumatoid arthritis (RA) one study found inverse associations between increasing level of self-reported physical activity and AIx, in line with our results (15). Another study on RA found that higher CRF was associated with a better CVD risk profile; however arterial stiffness was not an outcome (16). We have previously published results from a randomized controlled trial evaluating the effects of high intensity exercise in patients with AS showing significant treatment effects on both VO_2peak (increased) and arterial stiffness (decreased), although, due to the low sample size, associations between the changes of these parameters were not evaluated (17).

CRF is determined by genes, age, gender, physical activity, smoking, obesity and medical conditions, where physical activity is the most important lifestyle factor (4). In the general population there is a dose-response relation between physical activity and CRF where physical activity/exercise at moderate and high intensity results in improvement of CRF. Thus, CRF is a marker of habitual physical activity (4).

The arterial stiffness is determined by the functional and structural properties of the arterial wall. Traditional CVD risk factors (hypertension, hypercholesterolemia, BMI and smoking) and IJD are associated with increased arterial stiffness (18). Moreover, regular aerobic high intensity exercise can reduce arterial stiffness in healthy adults and patients with increased risk of CVD (19). Regular aerobic exercise can affect both functional and structural components of the arterial wall, and approximately 40% of the CVD risk reduction of aerobic exercise is believed to be attributed to improved vascular hemodynamic properties, including arterial stiffness (8;19).

Accordingly, regular exercises may be an important factor behind the associations between CRF and arterial stiffness measurements in the present study. In studies of the general population improvement of CRF (where the participants increased the amount of exercise), has been associated with lower risk of CVD (4). Therefore, high intensity exercises aiming at improving CRF, may be an attractable way to reduce arterial stiffness and CVD risk in patients with AS.

Our group has previously published results from the same AS cohort where disease-related complaints were barriers for physical activity (20), and disease activity (ASDAS) was inversely associated with CRF (3). Accordingly, high disease activity may result in less physical activity and reduced CRF which in turn is associated with increased risk of CVD. Reducing disease activity by optimal medical treatment may facilitate increased amount of exercise at intensities needed to increase CRF and thereby reducing CVD risk.

There are some limitations of our study. This is a cross-sectional study, and the results are associations and cannot indicate causality. There may be bidirectional effects; high CRF may reduce the arterial stiffness by mechanisms mentioned previously, but increased arterial stiffness may also reduce CRF through increased systolic heart load, limiting cardiac output and thus reducing VO_2peak (11). However, repeating the analyses after exclusion of patients with CVD did not alter the results, indicating that established CVD is not the only factor explaining the association between CRF and arterial stiffness. Ideally, VO_2peak should have been measured by direct gas-analyses during a maximal exercise test. However, estimation of VO_2peak by an indirect maximal exercise test is regarded as the second best test and is considered as an acceptable test of CRF in research. The validity has been tested by comparing the estimated with direct measurement of VO_2peak (5). Estimation of VO_2peak may be difficult in patients with physical disabilities, e.g. arthritis in joints of the lower limbs, and may result in underestimation of VO_2peak. However, 98% of the patients reported reaching ≥17 on Borgs scale, indicating that the majority of patients exercised until exhaustion. Furthermore, the mean heart rate at the end of the exercise test (172 beats/minute) was close to the expected maximum heart rate (220 beats/minute minus age), which in this cohort is 171 beats/minute, suggesting that VO_2peak was not underestimated. Another important aspect is that we in the present study have analysed associations between biomarkers; VO_2peak (marker of CRF), and arterial stiffness (marker of CVD risk). Biomarkers only mirror some aspects of the truth, and conclusions must be drawn with caution. Clinical cardiovascular endpoints would have been more

optimal endpoints, but would not be achievable this cohort with a mean age of 49 years and with a sample size of 118 patients.

In conclusion, we found that low VO_2peak was associated with higher arterial stiffness in patients with AS, indicating that low CRF is associated with increased CVD risk. The clinical implication of this association may be that CVD risk can be reduced by increasing CRF in patients with AS, but longitudinal intervention studies analysing the effect of exercises improving CRF upon CVD risk in AS are warranted.

Reference List

(1) Fongen C, Halvorsen S, Dagfinrud H. High disease activity is related to low levels of physical activity in patients with ankylosing spondylitis. Clin Rheumatol 2013;32:1719-25.

(2) Passalent LA, Soever LJ, O'Shea FD, Inman RD. Exercise in ankylosing spondylitis: discrepancies between recommendations and reality. J Rheumatol 2010;37:835-41.

(3) Halvorsen S, Vøllestad NK, Fongen C, Provan SA, Semb AG, Hagen KB, et al. Physical fitness in patients with ankylosing spondylitis: comparison with population controls. Phys Ther 2012;92:298-309.

(4) Lee DC, Artero EG, Sui X, Blair SN. Mortality trends in the general population: the importance of cardiorespiratory fitness. J Psychopharmacol 2010;24 Suppl 4:27-35.

(5) American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescriptions. 9 ed. Lippincott Williams & Wilkins; 2014.

(6) Church TS, Lamonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med 2005;165:2114-20.

(7) Papagoras C, Voulgari PV, Drosos AA. Atherosclerosis and cardiovascular disease in the spondyloarthritides, particularly ankylosing spondylitis and psoriatic arthritis. Clin Exp Rheumatol 2013;31:612-20.

(8) Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension 2015;66:698-722.

(9) Bodnár N, Kerekes G, Seres I, Paragh G, Kappelmayer J, Némethné ZG, et al. Assessment of subclinical vascular disease associated with ankylosing spondylitis. J Rheumatol 2011;38:723-9.

(10) Berg IJ, van der Heijde D, Dagfinrud H, Seljeflot I, Olsen IC, Kvien TK, et al. Disease activity in ankylosing spondylitis and associations to markers of vascular pathology and traditional cardiovascular disease risk factors: a cross-sectional study. J Rheumatol 2015;42:645-53.

(11) Binder J, Bailey KR, Seward JB, Squires RW, Kunihiro T, Hensrud DD, et al. Aortic augmentation index is inversely associated with cardiorespiratory fitness in men without known coronary heart disease. Am J Hypertens 2006;19:1019-24.

(12) Boreham CA, Ferreira I, Twisk JW, Gallagher AM, Savage MJ, Murray LJ. Cardiorespiratory fitness, physical activity, and arterial stiffness: the Northern Ireland Young Hearts Project. Hypertension 2004;44:721-6.

(13) Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.

(14) van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811-8.

(15) Crilly MA, Wallace A. Physical inactivity and arterial dysfunction in patients with rheumatoid arthritis. Scand J Rheumatol 2013;42:27-33.

(16) Metsios GS, Koutedakis Y, Veldhuijzen van Zanten JJ, Stavropoulos-Kalinoglou A, Vitalis P, Duda JL, et al. Cardiorespiratory fitness levels and their association with cardiovascular profile in patients with rheumatoid arthritis: a cross-sectional study. Rheumatology 2015;54:2215-20.

(17) Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB, Vøllestad N, et al. Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. PLoS One 2014;9:e108688.

(18) Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588-605.

(19) Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2014;9:e110034.

(20) Fongen C, Sveaas SH, Dagfinrud H. Barriers and Facilitators for Being Physically Active in Patients with Ankylosing Spondylitis: A Cross-sectional Comparative Study. Musculoskeletal Care 2015;13:76-83.

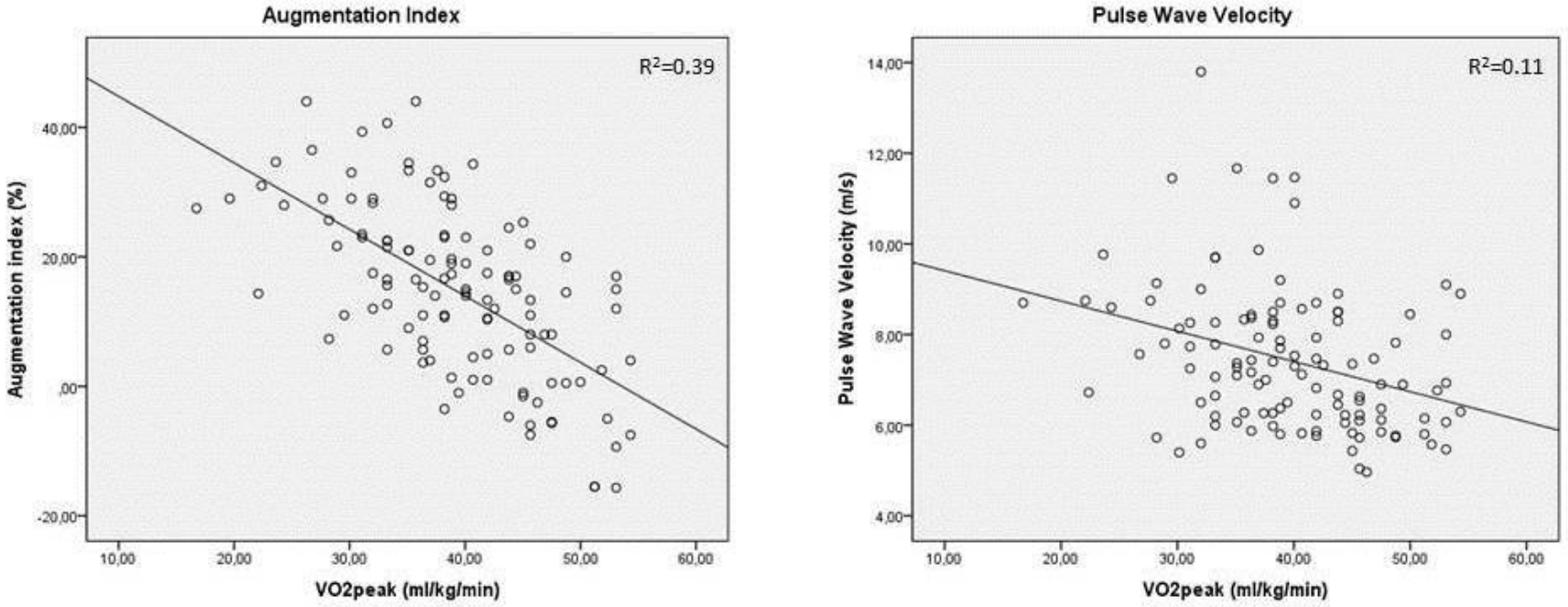
Table 1 Descriptives of the patients

Demographics	**n=118**
Age (years), mean (SD)	48.9 (11.2)
Gender (male), n (%)	75 (64)
Current smoking, n (%)	18 (15)
BMI (kg/m^2), mean (SD)	25.6 (3.4)
Height (cm), mean (SD)	174 (10)
Loss of height (cm), median (IQR)	1 (0, 3)
Disease characteristics	
BASDAI, mean (SD)	3.7 (1.8)
ASDAS, mean (SD)	2.3 (0.9)
CRP (mg/l), median (IQR)	3 (1, 9)
Medication, current use	
NSAIDs, n (%)	77 (65)
TNFα-inhibitors, n (%)	24 (20)
Statins, n (%)	15 (13)
Antihypertensives, n (%)	28 (24)
Lipids	
TC (mmol/l), mean (SD)	5.4 (1.1)

HDL-c (mmol/l), mean (SD)	1.6 (0.5)
Cardiorespiratory fitness	
VO_2peak (ml/kg/min), mean (SD)	39.3 (8.0)
Maximum heart rate (beats/min), mean (SD)	172 (19)
Borgs scale ≥ 17 at end of exercise test, n (%)	115 (98)
Hemodynamic	
Brachial SBP (mmHg), mean (SD)	127 (17)
Brachial DBP (mmHg), mean (SD)	78 (10)
CMAP (mmHg), mean (SD)	95 (12)
AIx (%), mean (SD)	14.8 (13.1)
PWV (m/s), median (IQR)	7.3 (6.2, 8.4)
Ln(PWV+0.5), mean (SD)	1.986 (0.199)

AIx, Augmentation Index; ASDAS, ankylosing spondylitis disease activity score; BMI, body mass index; CMAP, central mean arterial pressure; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-c high density lipoprotein cholesterol; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; PWV, pulse wave velocity; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TNFα, tumor necrosis factor alpha; VO_2peak; peak oxygen uptake.

Figure 1. Scatterplots cardiorespiratory fitness and arterial stiffness



Associations between VO_2peak and arterial stiffness measured as Augmentation Index and Pulse Wave Velocity with a regression line.

VO_2peak, peak oxygen uptake

Table 2 Associations between cardiorespiratory fitness and arterial stiffness, multivariable linear regression

	Outcome AIx				**Outcome lnPWV**			
	Univariate		Multivariable		Univariate		Multivariable	
	Beta (95%CI)	p-value	Beta (95%CI)	p-value	Beta (95%CI)	p-value	Beta (95%CI)	p-value
Age	0.8 (0.6, 0.9)	<0.001	0.5 (0.3, 0.6)	<0.001	0.012 (0.009, 0.014)	<0.001	0.009 (0.006, 0.012)	<0.001
Gender (male)	-12.5 (-16.9, -8.0)	<0.001	-9.4 (-12.6, -6.2)	<0.001	0.035 (-0.042, 0.113)	0.37	0.111 (0.046, 0.176)	0.001
VO_2peak (ml/kg/min)	-0.4 (-0.6, -0.2)[a]	0.002	-0.3 (-0.6, -0.1)	0.01	-0.003 (-0.007, 0.002)[a]	0.24	-0.005 (-0.010, -0.001)	0.03
Current smoking	0.7 (-3.6, 5.0)[a]	0.74			-0.072 (-0.147, 0.003)[a]	0.06		
BMI (kg/m^2)	0.2 (-0.3, 0.6)[a]	0.44			0.007 (-0.001, 0.015)[a]	0.09		
CRP (mg/l)	0.1 (-0.1, 0.3)[a]	0.16			0.002 (-0.001, 0.005)[a]	0.28		
ASDAS	1.0 (-0.7, 2.7)[a]	0.25			0.010 (-0.022, 0.041)[a]	0.54		
NSAIDs	0.2 (-3.6, 3.1)[a]	0.89			-0.034 (-0.093, 0.026)[a]	0.26		
TC (mmol/l)	0.3 (-1.2, 1.8)[a]	0.67			0.032 (0.005, 0.059)[a]	0.02	0.028 (0.003, 0.053)	0.03
HDL-c (mmol/l)	-2.9 (-6.6, 0.8)[a]	0.12			-0.006 (-0.075, 0.063)[a]	0.86		

CMAP (mmHg)	0.3 (0.2, 0.4)[a]	<0.001	0.3 (0.1, 0.4)	<0.001	0.006 (0.003, 0.008)[a]	<0.001	0.004 (0.002, 0.007)	0.001
Height (cm)	-0.1 (-0.3, 0.1)[a]	0.18			NA	NA		
Loss of height (cm)	NA	NA			-0.011 (-0.020, -0.002)[a]	0.02	-0.011 (-0.020, -0.002)	0.02
R square			0.69				0.63	

Linear regression models with arterial stiffness as dependent variable.

[a]adjusted age and gender

AIx, Augmentation Index; ASDAS, ankylosing spondylitis disease activity score; BMI, body mass index; CMAP, central mean arterial pressure; CRP, C-reactive protein; HDL-c, high density lipoprotein cholesterol; NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; TC, total cholesterol; VO_2peak, peak oxygen uptake.

Supplementary file 1

Detailed information about estimation of cardiorespiratory fitness and arterial stiffness

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by indirect estimation of peak oxygen uptake (VO_2peak). The patients performed a maximal exercise test on a treadmill where the exercise intensity was increased in a standardized manner by increased inclination and speed (according to a modified Balke protocol) until exhaustion (1). This is a validated test for estimating VO_2peak according to the American College of Sports Medicine's Guidelines for Exercise Testing and Prescriptions (2).

Before the test, the patients had a five minute warm up walking on the treadmill. At the start of the test the treadmill speed was set at an individually adapted speed based on the heart rate during the warm up, usually at 4.8 km/h and with a 2.5% inclination. The heart rate was recorded during the test (Polar Sports Tester). Each cycle lasted for one minute, and at the end of the cycle the patient evaluated the degree of perceived exertion on Borgs scale (range 6-10, where 6-very, very light and 20 - maximum exertion) (3). At the beginning of the test, the inclination was increased by 1.5% after every cycle and the speed was kept constant. When the patients reached an inclination of 15%, the speed was increased by 0.3 km/h by every cycle. The test was ended when the patient reported not being able to increase neither inclination nor speed and reported to be at 17-20 on Borgs scale. The maximum heart rate was recorded at the end of the test.

The VO_2peak was finally calculated by a formula given by the American College of Sports Medicine, from maximum speed (m/s) and inclination (%) by the end of the test, see textbox (4).

Graded walking (speeds ≤8.0 km/h):
VO_2 ml·kg^{-1}·min^{-1} = (0.1·ms^{-1}+1.8·ms^{-1}·inclination (%) +3.5)

Graded running (speeds >8.0 km/h):
VO_2 ml·kg^{-1}·min^{-1} = (0.2·ms^{-1}+0.9·ms^{-1}·inclination (%) +3.5)

Arterial stiffness

Arterial stiffness was assessed both as pulse wave velocity (PWV) and augmentation index (AIx). The measurements were performed under similar and well defined conditions; the patients were fasting (except from water) and non-smoking for the last three hours and had not used alcohol for the last 24 hours, the examinations were performed at the same time of the day in a quiet temperature-controlled room after at least 5 minutes supine rest (5). The measurements were performed using Sphygmocor Apparatus (AtCor Medical, Australia), following recommendations from AtCor Medical.

The PWV was measured as carotid femoral PWV which is considered as a golden standard measurement of the arterial stiffness (5). The PWV is a measure of the speed of the pulse wave, and was calculated my measuring the distance between the carotid pulse and the femoral pulse and the pulse transit time to these sites assessed by an electrocardiogram and pulse tonometry at the carotid and femoral artery. Finally, the PWV was calculated as distance divided by time, expressed in m/s.

The AIx is a surrogate measure of arterial stiffness, and was assessed through pulse wave analyses (5). The shape of the pulse wave was recorded at the radial artery by tonometry, and the shape of the central pulse wave was estimated through a validated transfer factor. The pulse pressure of the central pulse wave is generated from a forward pressure from the heart and a backwards reflected pressure from the peripheral arteries. The difference between the pulse pressure and the forward pressure is defined as the augmented pressure. AIx was finally expressed by calculating the augmented pressure as a percentage of the pulse pressure.

Reference List

(1) Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. U S Armed Forces Med J 1959;10:675-88.

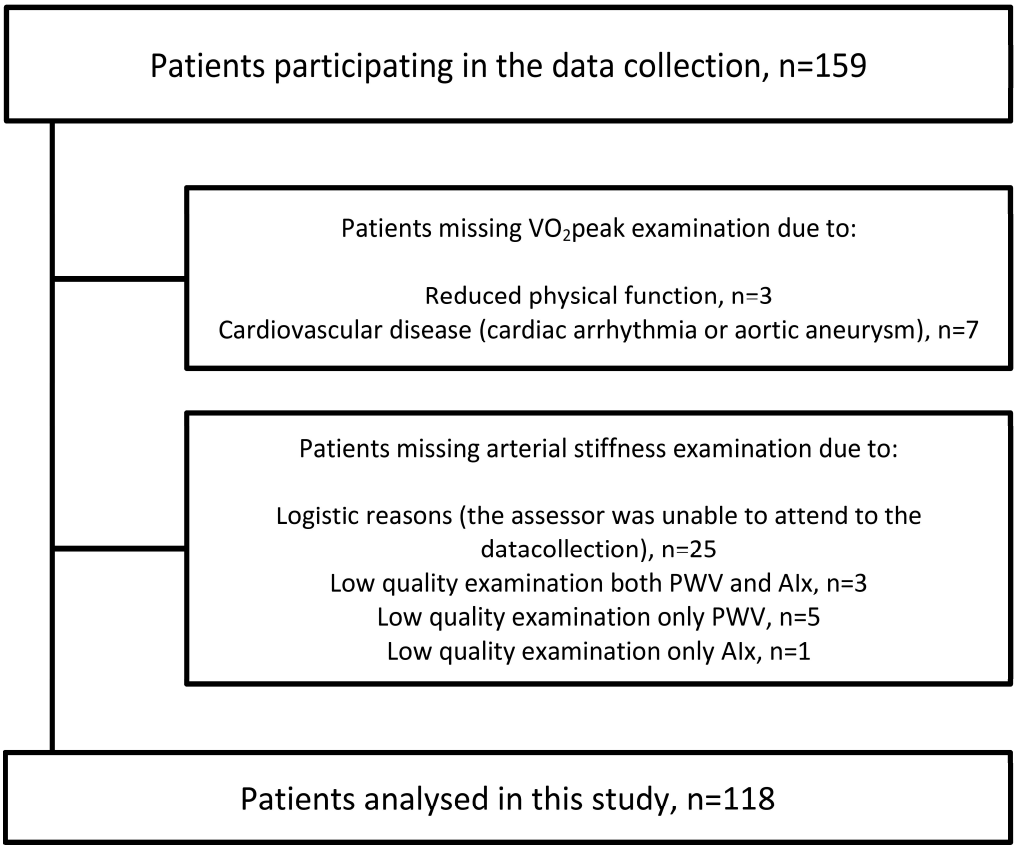
(2) American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescriptions. 9 ed. Lippincott Williams & Wilkins; 2014.

(3) Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2:92-8.

(4) American College of Sports Medicine. ACSM's Guidelines for exercise testing and prescription. 7 ed. New York: Lippincott Williams and Wilkins; 2006.

(5) Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588-605.

Supplementary Figure S1. Flowchart of the participants



Some patients have missing data for multiple assessments.