IJC Heart & Vasculature 23 (2019) 100347

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Association between resting heart rate, VO_2max and carotid intima-media thickness in middle-aged men

Seol-Jung Kang [a], Kwang-Jun Ko [b,*]

[a] Department of Physical Education, Changwon National University, Republic of Korea
[b] Department of Sports Medicine, National Fitness Center, Republic of Korea

ARTICLE INFO

Article history:
Received 11 February 2019
Received in revised form 13 March 2019
Accepted 17 March 2019
Available online 29 March 2019

Keywords:
Resting heart rate
VO_2max
Carotid intima-media thickness
Carotid atherosclerosis

ABSTRACT

Introduction: Low resting heart rate (RHR) and high cardiorespiratory fitness (VO_2max) are associated with a reduction in cardiovascular events (CV). Carotid intima-media thickness (CIMT) has been suggested as a predictor of CV. The purpose of this study was to investigate the association between RHR, VO_2max and CIMT.
Methods: The subjects of this study were 707 males aged 40–50 who visited the National Health Center of South Korea, a health examination institution, from 2010 to 2016. RHR was measured using electrocardiogram. RHR was divided into 4 levels (<60 beats per minute; bpm, 60–69 bpm, 70–79 bpm, ≥80 bpm). VO_2max was measured by grade exercise test. Subject's VO_2max was divided into 3 levels (first, second and third tertiles). CIMT was measured by B-mode ultrasound. Carotid atherosclerosis was defined as CIMT >1 mm.
Results: There was no significant difference in CIMT according to RHR level and there was no correlation between RHR and CIMT. High and middle VO_2max group had significant lower CIMT than low VO_2max group ($P < 0.001$). There was also a correlation between VO_2max and CIMT ($R = -0.129$, $P < 0.001$). The low VO_2max group showed 3.56-fold (95% CI, 1.77–7.16) higher relative risk of carotid atherosclerosis than the high VO_2max group.
Conclusion: These results suggest that cardiovascular fitness index VO_2max is associated to CIMT in middle-aged men. In addition, this study shows that VO_2max are important indicators for the prevalence of carotid atherosclerosis.

1. Introduction

The standard method for evaluating cardiovascular function is the resting heart rate (RHR) and maximum oxygen uptake (VO_2max). RHR is controlled by the interaction of the sympathetic and parasympathetic nerves of the autonomic nervous system. The autonomic nervous system maintains homeostasis regardless of changes in the internal environment. However, increased heart rate due to sympathetic nervous system hyperactivity causes cardiovascular dysfunction [1]. VO_2max is a single predictor of cardiorespiratory fitness or exercise capacity estimates and has a protective effect on cardiovascular disease [2]. It has been shown by several epidemiological studies that high RHR and low VO_2max play a role in increasing the risk of cardiovascular disease [3–6].

The onset of cardiovascular diseases is due to atherosclerosis. Although atherosclerosis is a major cause of coronary artery and cerebral artery disease, it is not easy to diagnose until clinical symptoms occur. Recently, carotid intima-media thickness (CIMT) test has been suggested to be useful in the diagnosis of atherosclerosis [7]. The American Heart Association [8] suggests CIMT as an independent influence factor of cardiovascular disease risk. A number of studies have also shown that CIMT is associated with cardiovascular risk factors [9–12]. In addition, according to the study of atherosclerosis risk in communities [13], the risk of coronary artery disease was 1.85-fold higher for men and 5.07-fold higher for women when the CIMT was >1 mm. Lorenz et al. [14] also found that the risk of myocardial infarction and stroke by 10 to 15% and 13 to 18%, respectively, when CIMT increased by 0.1 mm.

Thus, the CIMT is predictive of the risk of cardiovascular disease as a marker of atherosclerosis. In this respect, it is necessary to examine the association between RHR, VO_2max which is an index of cardiovascular function and CIMT. Therefore, this study aims to investigate the association between RHR, VO_2max and CIMT in healthy middle-aged men. We also examined the relative risk of carotid atherosclerosis according to the RHR and VO_2max level.

2. Methods

2.1. Subjects

This study was performed in 707 middle-aged men who visited the National Health Fitness Center of South Korea from Jan. 2010 to Dec. 2016 for health screening, carotid CIMT and exercise test. All subjects were surveyed for smoking, drinking, exercise, past illness and current

* Corresponding author at: National Fitness Center, Department of Sports Medicine, Olympic-ro 424, Songpa-gu, Seoul 05540, Republic of Korea.
E-mail address: tigerkor80@naver.com (K.-J. Ko).

https://doi.org/10.1016/j.ijcha.2019.100347

Table 1
Differences in physical characteristics, cardiovascular disease risk factors and CIMT depending on RHR.

RHR (bpm)	<60 (n = 353)	60–69 (n = 267)	70–79 (n = 66)	≥80 (n = 21)	*P*-value
	53.30 + 4.45	63.60 ± 2.64	73.62 ± 2.83	87.47 ± 7.62	
VO_2max (ml/kg/min)	43.31 ± 6.78	41.05 ± 5.93	40.42 ± 6.75	38.00 ± 7.00	0.001
Age (years)	48.38 ± 4.68	48.41 ± 4.73	48.70 ± 4.93	50.38 ± 5.39	0.295
Height (cm)	170.23 ± 5.67	169.97 ± 5.49	169.05 ± 4.75	169.95 ± 5.81	0.460
Weight (kg)	69.66 ± 8.30	70.42 ± 9.14	68.14 ± 8.79	70.97 ± 8.74	0.239
BMI (kg/m^2)	24.02 ± 2.43	24.34 ± 2.63	23.84 ± 2.93	24.57 ± 2.89	0.278
Exercise status (%)	225 (63.7)	145 (54.3)	33 (50.0)	11 (52.4)	0.174
Smoking status (%)	128 (36.3)	94 (35.2)	24 (36.4)	6 (28.6)	0.908
Drinking status (%)	297 (84.1)	223 (83.5)	45 (68.2)	17 (81.0)	0.017
SBP (mm Hg)	120.93 ± 14.09	126.01 ± 15.05	128.94 ± 14.71	134.81 ± 15.31	0.001
DBP (mm Hg)	74.64 ± 10.92	79.09 ± 11.04	81.71 ± 12.26	84.00 ± 10.46	0.001
T-Chol (mg/dL)	185.27 ± 33.48	187.46 ± 33.93	177.02 ± 29.33	178.19 ± 34.87	0.106
TG (mg/dL)	116.90 ± 59.34	130.79 ± 66.74	121.62 ± 59.52	159.05 ± 90.99	0.003
LDL-C (mg/dL)	107.25 ± 30.43	107.28 ± 30.40	98.90 ± 28.05	95.00 ± 25.85	0.057
HDL-C (mg/dL)	54.64 ± 11.75	54.01 ± 10.80	53.79 ± 10.57	51.38 ± 11.88	0.573
FBG (mg/dL)	87.25 ± 14.64	89.07 ± 13.19	94.64 ± 19.97	101.43 ± 23.57	0.001
AST (IU/L)	24.46 ± 15.87	24.07 ± 12.62	21.98 ± 11.75	20.42 ± 7.59	0.385
ALT (IU/L)	25.88 ± 18.79	28.89 ± 22.28	26.86 ± 23.81	24.32 ± 13.73	0.300
γ-GTP (IU/L)	36.99 ± 27.40	46.47 ± 46.02	41.78 ± 35.81	48.88 ± 39.48	0.113
CIMT (mm)	0.65 ± 0.20	0.67 ± 0.23	0.67 ± 0.24	0.70 ± 0.22	0.343

Data shown as Mean ± SD or n (%).
Exercise status: ≥30 min/day on ≥3 day/week, Smoking status: ≥1 cigarettes daily, Drinking status: ≥once/month.
RHR: resting heart rate, bpm: beats per minute, VO_2max: maximal oxygen uptake, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, T-Chol: total cholesterol, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, FBG: fasting blood glucose. AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma glutamyl transpeptidase, CIMT: carotid intima media thickness.
Tested by ANOVA or chi-square test.

medications. The exclusion criteria for this study were cardiovascular disease patients and those taking medicines that affect heart rate. This study was conducted after obtaining approval from the Institutional Review Board of Changwon University (IRB No. 1040271-201706-HR-101).

2.2. Anthropometry, blood pressure measure and blood test

Subject's height and weight were measured using an automatic anthropometric instrument (SH-9600A, Korea). Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$. Blood pressure was measured using systolic blood pressure and diastolic blood pressure (SBP, DBP) using an automatic blood pressure monitor (FT-500R, Jawon, Korea). Blood samples were collected from the brachial vein under fasting conditions for >10 h and analyzed with a biochemical analyzer (Selecta XL, Vital scientific, Newton, USA). The analysis items included total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (γ-GPT).

2.3. RHR and VO_2max measures

RHR was measured using a standard 12 lead automatic cardiac transducer (Cardiocare, Korea) after 10 min rest. The cardiorespiratory fitness test (grade exercise text; GXT) was carried out using an automatic breathing gas analysis system (Q4500, Quinton, Bothell, WA, USA) to determine the maximum oxygen uptake (VO_2max). The protocol for testing exercise loads was the modified Balke protocol. The criteria for ending the exercise load test were when the oxygen consumption did not increase even when the exercise load was increased, when the exercise self-conscious level was 17 or higher, when the heart rate was ±5 than the age-dependent predicted maximum heart rate by age, and when the respiratory exchange rate was higher than 1.15.

2.4. CIMT and carotid atherosclerosis diagnostic criteria

CIMT was measured by B-mode ultrasound (LOGIQ 3, GE Healthcare, Wisconsin, USA). CIMT was measured on the far wall of the distal common carotid artery 1 cm proximal to the carotid bulb. CIMT was defined as the distance from the luminal-intima interface to the medial-adventitial interface. In the present study, carotid atherosclerosis was defined as the CIMT above 1 mm with reference to the previous study [15,16].

2.5. Statistical analysis

Statistical analysis was performed using SPSS Win (version, 18.0). One-way ANOVA were performed to determine the difference in CIMT according to RHR, VO_2max. Subjects were divided into 4 levels of RHR

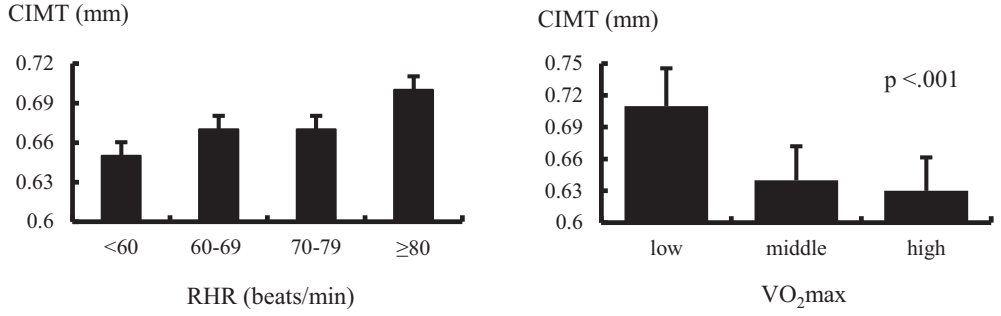

Fig. 1. CIMT according to levels of resting heart rate, VO_2max. CIMT: carotid intima-media thickness, RHR: resting heart rate.

Table 2
Differences in physical characteristics, cardiovascular disease risk factors and CIMT depending on VO_2max.

VO_2max (ml/kg/min)	Low (n = 238)	Middle (n = 231)	High (n = 238)	*P*-value
	34.82 ± 3.70	42.19 ± 1.57	49.05 ± 3.47	
RHR (bpm)	61.67 ± 9.33	60.61 ± 8.79	58.05 ± 8.68	0.001
Age (years)	49.46 ± 5.02	48.79 ± 4.80	47.21 ± 4.09	0.001
Height (cm)	170.49 ± 5.34	170.38 ± 5.76	169.20 ± 5.43	0.019
Weight (kg)	72.94 ± 9.20	69.78 ± 8.15	66.90 ± 7.61	0.001
BMI (kg/m^2)	25.07 ± 2.81	24.02 ± 2.35	23.34 ± 2.20	0.001
Exercise status (%)	108 (45.4)	79 (34.2)	67 (28.2)	0.019
Smoking status (%)	123 (51.7)	144 (62.3)	150 (63.0)	0.001
Drinking status (%)	198 (83.2)	200 (86.6)	187 (78.6)	0.074
SBP (mm Hg)	125.09 ± 15.31	124.10 ± 14.95	122.77 ± 14.42	0.231
DBP (mm Hg)	78.06 ± 10.78	77.40 ± 11.98	76.31 ± 11.37	0.237
T-Chol (mg/dL)	189.18 ± 33.15	184.72 ± 35.03	181.72 ± 32.58	0.051
TG (mg/dL)	144.13 ± 64.90	123.08 ± 62.56	104.77 ± 57.69	0.001
LDL-C (mg/dL)	105.95 ± 29.98	106.29 ± 32.17	106.39 ± 29.19	0.987
HDL-C (mg/dL)	54.41 ± 10.74	53.81 ± 11.68	54.38 ± 11.42	0.813
FBG (mg/dL)	91.78 ± 18.22	88.92 ± 14.92	86.57 ± 11.74	0.001
AST (IU/L)	25.43 ± 19.43	22.91 ± 11.14	23.46 ± 9.72	0.126
ALT (IU/L)	30.49 ± 24.86	25.77 ± 19.87	24.93 ± 15.43	0.006
γ-GTP (IU/L)	49.88 ± 46.95	38.98 ± 30.44	35.55 ± 29.11	0.001
CIMT (mm)	0.71 ± 0.26	0.64 ± 0.19	0.63 ± 0.18	0.001

Data shown as Mean ± SD or n (%).
Exercise status: ≥30 min/day on ≥3 day/week, Smoking status: ≥1 cigarettes daily, Drinking status: ≥once/month.
RHR: resting heart rate, bpm: beats per minute, VO_2max: maximal oxygen uptake. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, T-Chol: total cholesterol, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, FBG: fasting blood glucose. AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma glutamyl transpeptidase, CIMT: carotid intima-media thickness.
Tested by ANOVA or chi-square test.

(<60 beats per minute; bpm, 60–69 bpm, 70–79 bpm, and ≥80 bpm) for analysis. VO_2max was divided into 3 levels. Subjects in the lowest tertile (≤33.3%) had low VO_2max, those in the second tertile (>33.3%, ≤66%) had middle VO_2max, and those in the highest tertile (>66.6%) had high VO_2max.

The correlations between RHR, VO_2max and CIMT were correlated with age, smoking status, drinking status, and exercise status as covariates. In addition, logistic regression analysis was performed to calculate the relative odds ratio of carotid atherosclerosis according to RHR, VO_2max. The statistical significance level (α) was set at $P < 0.05$.

3. Results

3.1. Difference in cardiovascular disease risk factors and CIMT according to RHR

There was a significant difference VO_2max ($P < 0.001$), DBP ($P < 0.001$), TG ($P < 0.01$), and fasting blood glucose ($P < 0.001$) according to the RHR. However, there were no significant differences in BMI, total cholesterol, LDL-C, HDL-C, AST, AST, and γ-GTP. Also there was no significant difference between RHR and CIMT (Table 1, Fig. 1).

Table 4
Odds ratio of having the carotid atherosclerosis according to levels of resting heart rate.

Resting heart rate (bpm)	Carotid atherosclerosis			
	Unadjusted OR	(95% CI)	Adjusted OR	(95% CI)
<60	1.00		1.00	
60–69	1.49	0.80–2.75	1.12	0.61–2.41
70–79	2.18	0.92–5.15	2.10	0.75–5.86
≥80	1.66	0.36–7.62	0.92	0.17–4.98

OR: odds ratio.
Adjusted for age, body mass index, exercise, smoking, drinking status, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fasting blood glucose.

3.2. Difference in cardiovascular risk factors and CIMT according to VO_2max

There was a significantly different in RHR ($P < 0.001$), BMI ($P < 0.001$), TG ($P < 0.001$), fasting blood glucose ($P < 0.001$), ALT ($P < 0.01$), and γ-GTP ($P < 0.001$) according to the VO_2max. However, SBP, DBP, total cholesterol, LDL-C, HDL-C, and AST were not significantly different. In addition high and middle VO_2max group had significant lower CIMT than low VO_2max group (0.63 ± 0.81 mm; 0.64 ± 0.19 mm; 0.71 ± 0.26 mm, $P < 0.001$) (Table 2, Fig. 1).

3.3. Correlation between cardiovascular function, cardiovascular disease risk factors and CIMT

RHR was positively correlated with SBP ($R = 0.257$, $P < 0.001$), DBP ($R = 0.268$, $P < 0.001$), TG ($R = 0.127$, $P < 0.001$), fasting blood glucose ($R = 0.171$, $P < 0.001$), and γ-GTP ($R = 0.123$, $P < 0.001$). There was no correlation between BMI, total cholesterol, LDL-C, HDL-C, AST, ALT and CIMT.

VO_2max was significantly correlated with BMI ($R = -0.282$, $P < 0.001$), SBP ($R = -0.081$, $P < 0.05$), DBP ($R = -0.011$, $P < 0.05$), TG ($R = -0.239$, $P < 0.001$), fasting blood glucose ($R = -0.094$, $P < 0.001$), and CIMT ($R = -0.129$, $P < 0.001$), respectively. On the other hand, there was no correlation between LDL-C, HDL-C and AST (Table 3).

3.4. Relative risk of carotid atherosclerosis according to RHR, VO_2max

There was no significant difference in the relative risk of carotid atherosclerosis according to the RHR levels (Table 4). The relative risk of carotid atherosclerosis was 3.56-fold (95% CI, 1.77–7.16) higher in the lower group than in the group with higher VO_2max (Table 5).

4. Discussion

In this study, we analyzed the association between RHR, VO_2max and CIMT in healthy adult males. As a result, there was no significant difference between the RHR level and CIMT. Also there was no correlation between RHR and CIMT. On the other hand, high VO_2max showed a decreased in CIMT compared low VO_2max, and there was also association between VO_2max and CIMT.

Table 3
Correlation of between RHR, VO2max and cardiovascular disease risk factors, CIMT.

Variables		BMI	SBP	DBP	T-Chol	TG	LDL-C	HDL-C	FBG	AST	ALT	γ-GTP	CIMT
RHR	r	0.038	0.257	0.268	−0.016	0.127	−0.061	−0.027	0.171	−0.037	0.052	0.123	0.045
	P	0.319	0.001	0.001	0.669	0.001	0.109	0.473	0.001	0.323	0.167	0.001	0.230
VO_2max	r	−0.282	−0.081	−0.079	−0.080	−0.239	0.012	−0.004	−0.094	−0.011	−0.096	−0.134	−0.129
	P	0.001	0.032	0.037	0.034	0.001	0.747	0.911	0.012	0.770	0.011	0.001	0.001

RHR: resting heart rate, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, T-Chol: total cholesterol, TG: triglycerides, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, FBG: fasting blood glucose. AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: gamma glutamyl transpeptidase, CIMT: carotid intima-media thickness.
Adjusted for age, exercise, smoking and drinking status.

Table 5
Odds ratio of having the carotid atherosclerosis according to levels of VO_2max.

VO_2max	Carotid atherosclerosis			
	Unadjusted OR	(95% CI)	Adjusted OR	(95% CI)
High	1.00		1.00	
Middle	0.76	0.31–1.84	0.78	0.32–1.89
Low	3.13	1.58–6.22	3.56	1.77–7.16

OR: odds ratio.
Adjusted for age, body mass index, exercise, smoking, drinking status, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fasting blood glucose.

RHR can be used to determine the autonomic nervous system activity that regulates cardiovascular function and high RHR promotes cardiovascular diseases [17]. Cardiorespiratory fitness is assessed as VO_2max and low VO_2max increases the risk of cardiovascular diseases [18]. The carotid artery is a blood vessel that connects the cerebral blood vessels with the aorta from the heart. Previous studies have shown that intima-media walls of the carotid artery are at increased risk for exposure to cardiovascular disease. Also it has been reported that the risk of coronary artery disease and stroke is increased when the CIMT is >1 mm [13,14,19]. CIMT measurement with B-mode ultrasound is useful for cardiovascular disease assessment and prognostic evaluation.

We found that higher the RHR level, the more CIMT was increased but the difference was not significant. There was no association between RHR and CIMT. In other words, RHR changes did not affect ICMT in this study. On the other hand, Wang et al. [20] found that RHR in middle-aged and older adults over 50 years of age are associated CIMT. The relative risk of carotid atherosclerosis according to RHR was 2.82-fold higher at 81 bpm than at 67 bpm. Also, in previous studies, heart rate variability analysis of cardiac autonomic nervous system activity has also been associated with CIMT [21,22]. This suggests that high RHR due to sympathetic hyperactivity affects the increase of CIMT. However, additional research is needed to understand the direct association between RHR and ICMT. In addition, in the present study, the difference in CIMT according to the RHR was not observed because the number of subjects with RHR of 70–80 bpm, 80 bpm or more was small.

Meanwhile, the results of this study showed that the lower the VO_2max level, the higher the CIMT and VO_2max showed a significant negative correlation with ICMT. The relative risk of carotid atherosclerosis was 3.56-fold higher at low VO_2max than at high levels of VO_2max. Previous studies have shown that high levels of the VO_2max, lowered the CIMT [23,24]. Rauramaa et al. [25] found association between VO_2max and CIMT. In addition low cardiorespiratory fitness in patients with hypertension and type 2 diabetes have been associated with increased CIMT [26,27]. Furthermore, regular exercise has been reported to be effective in increasing cardiovascular function and reducing CIMT [28]. Considering the results of the previous studies and the results of this study, it can be seen that the VO_2max is related to ICMT. However, additional research is needed to understand the direct association between VO_2max and ICMT.

The limitation of this study is that it is difficult to generalize the association between RHR, VO_2max and CIMT in middle-aged men who visited a local health examination center. Also other variables such as diet, stress, etc. that affect the CIMT were not included. Moreover, in recent studies, methodological problems have been suggested in the evaluation of CIMT [29]. That is no precise criteria for the measurement site or measurement method of CIMT. Therefore, in future studies, it is important to consider standardization of measurement site selection and measurement method for CIMT analysis. However, this study has significance as a study that investigates cardiovascular fitness and ICMT relationship in healthy adult's men.

5. Conclusion

This study showed that RHR, which reflects cardiovascular function in middle-aged men is not associated with CIMT. On the other hand, VO_2max is associated with CIMT. Furthermore, low VO_2max has a high risk of relative incidence of carotid arteriosclerosis. The results of this study can provide the data on the importance of cardiorespiratory fitness in the prevention of CV.

Conflict of interest

The authors have no conflicts of interest to declare disclosure.

References

[1] B.M. Curtis, J.H. O'Keefe, Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight, Mayo Clin. Proc. 77 (2002) 45–54.
[2] P.T. Williams, Physical fitness and activity as separate heart disease risk factors: a meta-analysis, Med. Sci. Sports Exerc. 33 (2001) 754–761.
[3] S. Kurl, J.A. Laukkanen, R. Rauramaa, et al., Cardiorespiratory fitness and the risk for stroke in men, Arch. Intern. Med. 163 (2003) 1682–1688.
[4] X. Sui, M.J. LaMonte, S.N. Blair, Cardiorespiratory fitness as a predictor of nonfatal cardiovascular events in asymptomatic women and men, Am. J. Epidemiol. 165 (2007) 1413–1423.
[5] T.R. Wessel, C.B. Arant, M.B. Olson, et al., Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women, JAMA 292 (2004) 1179–1187.
[6] S. Kodama, K. Saito, S. Tanaka, et al., Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis, JAMA (2009) 2024–2035.
[7] S.H. Johnsen, E.B. Mathiesen, Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease, Curr. Cardiol. Rep. 11 (2009) 1–27.
[8] S.C. Smith Jr., P. Greenland, S.M. Grundy, AHA conference proceedings: prevention conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary, American Heart Association, Circulation 101 (2000) 111–116.
[9] P.H. Davis, J.D. Dawson, W.A. Riley, et al., Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age, Circulation 10 (2001) 2815–2819.
[10] S. Ebrahim, O. Papacosta, P. Whincup, et al., Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study, Stroke. 30 (1999) 841–850.
[11] A. Scuteri, S.S. Najjar, D.C. Muller, et al., Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness, J. Am. Coll. Cardiol. 43 (2004) 1388–1395.
[12] M. Tatsukawa, Y. Sawayama, N. Maeda, et al., Carotid atherosclerosis and cardiovascular risk factors: a comparison of residents of rural area of Okinawa with residents of a typical suburban area of Fukuoka, Japan, Atherosclerosis 172 (2004) 37–43.
[13] L.E. Chambless, G. Heiss, A.R. Folsom, et al., Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993, Am. J. Epidemiol. 146 (1997) 483–494.
[14] M.W. Lorenz, H.S. Markus, M.L. Bots, et al., Prediction of clinical cardiovascular events with carotid intima-media thickness: a systemic review and meta-analysis, Circulation 115 (2007) 459–467.
[15] L.E. Chambless, A.R. Folsom, L.X. Clegg, et al., Carotid wall thickness is predictive of incident clinical stroke, Am. J. Epidemiol. 151 (2000) 478–487.
[16] A. Simon, J. Gariepy, G. Chironi, et al., Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk, J. Hypertens. 20 (2002) 159–169.
[17] K. Fox, J.R. Borer, A.J. Camm, et al., Heart Rate Working Group. Resting heart rate in cardiovascular disease, J. Am. Coll. Cardiol. 50 (2007) 823–830.
[18] J.D. Berry, B. Willis, S. Gupta, et al., Lifetime risks for cardiovascular disease mortality by cardiorespiratory fitness levels measured at ages 45, 55, and 65 years in men: the cooper center longitudinal study, J. Am. Coll. Cardiol. 57 (2011) 1604–1610.
[19] M. Bots, A. Hoes, P. Koudstaal, et al., Common carotid intima-media thickness and risk of stroke and myocardial infarction. The Rotterdam Study, Circulation 96 (1997) 1432–1437.
[20] L. Wang, N. Zhang, B.G. Sun, et al., Elevated resting heart rate is associated with carotid atherosclerosis in middle-aged and elderly Chinese population, J. Stroke Cerebrovasc. Dis. 25 (2016) 34–40.
[21] V.L.J. Pereira, S.G. dos Santos, J.S. Fuzatti, et al., Subclinical carotid atherosclerosis is associated with alterations of time-domain indices of heart rate variability, J. Hypertens. 33 (2015) e258.
[22] V.L.J. Pereira, M. Dobre, S.G. dos Santos, et al., Association between carotid intima media thickness and heart rate variability in adults at increased cardiovascular risk, Front. Physiol. 8 (2017) 248.
[23] T.A. Lakka, J.A. Laukkanen, R. Rauramaa, et al., Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men, Ann. Intern. Med. 134 (2001) 12–20.
[24] Y. Gando, K. Yamamoto, H. Kawano, et al., Attenuated age-related carotid arterial remodeling in adults with a high level of cardiorespiratory fitness, J. Atheroscler. Thromb. 18 (2011) 248–254.
[25] R. Rauramaa, T. Rankinen, P. Tuomainen, et al., Inverse relationship between cardiorespiratory fitness and carotid atherosclerosis, Atherosclerosis. 112 (1995) 213–221.

[26] S.Y. Jae, M.R. Carnethon, K.S. Heffernan, et al., Association between cardiorespiratory fitness and prevalence of carotid atherosclerosis among men with hypertension, Am. Heart J. 153 (2007) 1001–1005.
[27] S.Y. Jae, K. Heffernan, B. Fernhall, et al., Cardiorespiratory fitness and carotid artery intima media thickness in men with type 2 diabetes, J. Phys. Act. Health 9 (2012) 549–553.
[28] H. Tanaka, D.R. Seals, K.D. Monahan, et al., Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men, J. Appl. Physiol. 92 (2002) 1458–1464.
[29] A. Maloberti, P. Meani, M. Varrenti, et al., Structural and functional abnormalities of carotid artery and their relation with EVA phenomenon, High. Blood. Press. Cardivasc. Prev. 22 (2015) 373–379.