

Association between resting heart rate, VO₂max and carotid intima-media thickness in middle-aged men

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ABSTRACT

Introduction: Low resting heart rate (RHR) and high cardiorespiratory fitness (VO₂max) 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, VO₂max 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). VO₂max was measured by grade exercise test. Subject's VO₂max 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 VO₂max group had significant lower CIMT than low VO₂max group ($P < 0.001$). There was also a correlation between VO₂max and CIMT ($R = -0.129$, $P < 0.001$). The low VO₂max group showed 3.56-fold (95% CI, 1.77–7.16) higher relative risk of carotid atherosclerosis than the high VO₂max group.

Conclusion: These results suggest that cardiovascular fitness index VO₂max is associated to CIMT in middle-aged men. In addition, this study shows that VO₂max are important indicators for the prevalence of carotid atherosclerosis.

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1. Introduction

The standard method for evaluating cardiovascular function is the resting heart rate (RHR) and maximum oxygen uptake (VO₂max). 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]. VO₂max 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 VO₂max 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, VO₂max which is an index of cardiovascular function and CIMT. Therefore, this study aims to investigate the association between RHR, VO₂max and CIMT in healthy middle-aged men. We also examined the relative risk of carotid atherosclerosis according to the RHR and VO₂max 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

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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 ₂ max (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, VO₂max: 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 VO₂max measures

RHR was measured using a standard 12 lead automatic cardiac transducer (Cardiocare, Korea) after 10 min rest. The cardiorespiratory fitness test (grade exercise test; GXT) was carried out using an

automatic breathing gas analysis system (Q4500, Quinton, Bothell, WA, USA) to determine the maximum oxygen uptake (VO₂max). 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, VO₂max. Subjects were divided into 4 levels of RHR

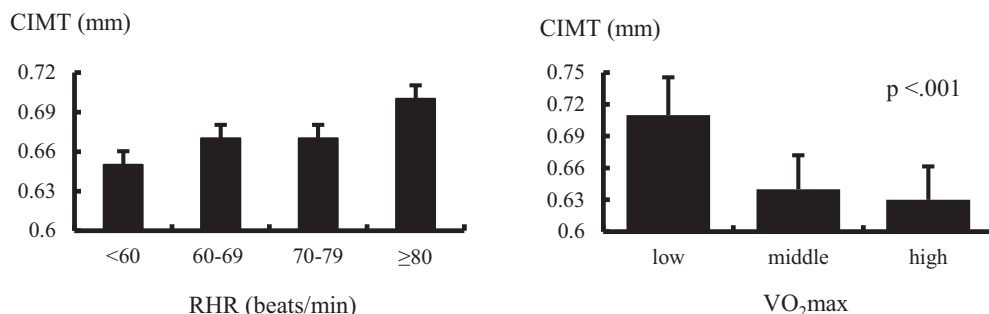


Fig. 1. CIMT according to levels of resting heart rate, VO₂max. CIMT: carotid intima-media thickness, RHR: resting heart rate.

Table 2Differences in physical characteristics, cardiovascular disease risk factors and CIMT depending on VO₂max.

VO ₂ max (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, VO₂max: 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. VO₂max was divided into 3 levels. Subjects in the lowest tertile (≤33.3%) had low VO₂max, those in the second tertile (>33.3%, ≤66%) had middle VO₂max, and those in the highest tertile (>66.6%) had high VO₂max.

The correlations between RHR, VO₂max 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, VO₂max. 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 VO₂max ($P < 0.001$), 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, ALT, and γ-GTP. Also there was no significant difference between RHR and CIMT (Table 1, Fig. 1).

Table 3Correlation 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 ₂ max	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 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 VO₂max

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 VO₂max. However, SBP, DBP, total cholesterol, LDL-C, HDL-C, and AST were not significantly different. In addition high and middle VO₂max group had significant lower CIMT than low VO₂max 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.

VO₂max 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, VO₂max

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 VO₂max (Table 5).

4. Discussion

In this study, we analyzed the association between RHR, VO₂max 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 VO₂max showed a decreased in CIMT compared low VO₂max, and there was also association between VO₂max and CIMT.

Table 5
Odds ratio of having the carotid atherosclerosis according to levels of VO₂max.

VO ₂ max	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 VO₂max and low VO₂max 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 VO₂max level, the higher the CIMT and VO₂max showed a significant negative correlation with ICMT. The relative risk of carotid atherosclerosis was 3.56-fold higher at low VO₂max than at high levels of VO₂max. Previous studies have shown that high levels of the VO₂max, lowered the CIMT [23,24]. Rauramaa et al. [25] found association between VO₂max 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 VO₂max is related to ICMT. However, additional research is needed to understand the direct association between VO₂max and ICMT.

The limitation of this study is that it is difficult to generalize the association between RHR, VO₂max 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,

VO₂max is associated with CIMT. Furthermore, low VO₂max 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.

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