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Original Article

Correlation of Resting Heart Rate with the Severity and Complexity of Coronary Artery Disease: A Single-Center Retrospective Study

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Abstract

Background: We aimed to explore the association between resting heart rate (RHR) and the severity and complexity of atherosclerosis in coronary artery disease (CAD). **Methods:** Clinical and laboratory data of 388 patients who underwent coronary angiography were evaluated retrospectively. SYNTAX and Gensini scores were calculated based on angiographic findings. These scores which indicate the severity of atherosclerosis was calculated for all the patients. Patients were divided into three main groups according to RHR. Group 1 composed of patients with RHR ≤70 (n = 217), group 2 composed of patients with RHR between 70 and 89 (n = 133), and group 3 composed of patients with RHR ≥90 beats per min (bpm) (n = 38). Gensini and SYNTAX score values of the three study groups were compared. Also, Gensini score was tested for whether it showed a positive correlation with RHR and SYNTAX scores. **Results:** All patients had an average age of 61.3 years, and the mean for RHR was 72 bpm. Mean Gensini score in the general CAD population was 24.4 ± 22.5, and mean SYNTAX score was 13.6 ± 8.1 points. The Gensini and Syntax score values of the group 3 were significantly higher than that of the other two groups (59.8 ± 31.2, $P < 0.001$ and 26.0 ± 6.5, $P < 0.001$, respectively). There was a significant correlation with Gensini score and RHR, SYNTAX score, C-reactive protein (CRP), and left ventricular ejection fraction [(r = 0.725, $P < 0.001$), (r = 0.680, $P < 0.001$), (r = 0.543, $P < 0.001$), (r = −0.224, $P < 0.001$), respectively]. **Conclusions:** RHR is an effective easily available marker for the assessment of severity and complexity of CAD.

Keywords: *Coronary artery disease, heart rate, the SYNTAX scores*

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality all over the world and the incidence of CAD has been increasing tremendously.[1] Diagnosis of silent CAD and defining the prognosis and cardiovascular risks (CVs) by non-invasive tests are of great importance. Resting heart rate (RHR), which is a simple and easily measurable clinical parameter, predicts both CV and non-CV death in general populations.[2,3] Epidemiological studies for a long time have found that elevated RHR may be associated with increased risk of all-cause mortality and CV mortality, both in the general population and in those with established CV disease.[4] Although relationship between traditional CV risk factors and CV events are clearly demonstrated, the guidelines of regarding risk factors were not observed in a proportion of patients with CAD.[5–7]

Increasing RHR had suggested that it can have effect directly on the arterial wall and encourage the development of atherosclerotic plaques. Present evidences and the basic mechanisms may suggest that RHR may be an independent risk factor.[8] Based on these findings, CAD in heart rate reduction with agents such as ivabradine or beta-blockers have been shown to decrease the mortality rate.[9]

Gensini scoring system is a method used to assess the prevalence of CAD. This system is known to be proportional to the severity of coronary atherosclerosis.[8,9] Gensini score is calculated via a formula considering severity of coronary artery stenosis and size of the area where the coronary arteries perfuse. Gensini scoring is an objective criterion in the diagnosis of severe CAD.[10,11]

The SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) score, which is an angiographic tool used in grading

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the complexity of CAD and the risks of percutaneous or surgical revascularization, has been considering the functional effect of the coronary circulation with all its anatomic components such as the presence of bifurcations, total occlusions, thrombus, calcification, and small vessels.[12]

Although heart rate and long-term prognosis of CAD have been mentioned in the literature,[2,3] there is no enough number of studies comparing pre-treatment RHR with severity and extent of CAD. In this aspect, this study will enlighten this gap in the literature.

In this study, it was aimed to evaluate the usefulness of RHR in predicting severity and complexity of coronary atherosclerosis expressed by the Gensini and SYNTAX score in patients with CAD undergone coronary angiography (CAG).

Methods

Study design and population

We consecutively enrolled a total of 388 patients who were admitted to our tertiary center outpatient clinic for stable angina pectoris with sinus rhythm and had at least one main coronary vessel with >50% luminal narrowing and indicated for CAG. All subjects were recruited from January 2016 to January 2018. All patients had stable anginal symptoms and/or positive myocardial perfusion scintigraphy or stress test results, or some electrocardiographic changes pointing to ischemia. Major exclusion criteria included patients with previous and acute myocardial infarction, history of coronary artery bypass graft surgery, history of previous percutaneous coronary intervention, congestive heart failure [left ventricular ejection fraction (EF) <50%], hypertrophic cardiomyopathy, valvular heart diseases, congenital heart disease, acute or chronic infectious disease, rheumatologic diseases, thyroid diseases, kidney or liver failure, and any psychiatric diseases. Other than these exclusion criteria, patients with a permanent pacemaker, atrial fibrillation or flutter, other arrhythmias, and patients who used heart rate-controlling drugs were also excluded from the study.

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the local ethics committee and written informed consent was obtained from all participants. Baseline demographic information, including age, sex, smoking status, hyperlipidemia, hypertension, diabetes mellitus (DM), family history and previous medications, systolic blood pressure (BP), diastolic BP, and body mass index (BMI) were obtained retrospectively in all patients. RHR measurements during the first clinical outpatient contact were taken from resting 12-lead electrocardiography (ECG). RHR was determined by performing routine 12-lead ECG after resting for 10 min. Patients were divided into three main groups according to RHR. Group 1 composed of patients with RHR ≤70 (n = 217), group 2 composed of patients with RHR between 70 and 89 (n = 133), and group 3 composed of patients with RHR ≥90 beats per min (bpm) (n = 38).[13]

Assessment of CAG, the Gensini score, and the SYNTAX score

CAG was performed via the Judkins technique through the femoral or radial artery access. Left anterior descending and left circumflex coronary arteries were evaluated in at least four angiographic views, while right coronary artery was being evaluated in at least two angiographic views. The angiographical severity of coronary stenosis was assessed in the position with the most luminal narrowing, and the percentage of luminal narrowing was recorded according to the American Heart Association reporting system.[14] A thorough analysis of each CAG established the lesion location and the percentage of stenosis. The Gensini scoring system was used to define the severity of the CAD.[10] The Gensini score is computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. The SYNTAX score, an anatomical scoring system to grade the complexity of CAD, was calculated for each patient accordingly. All coronary lesions resulting in luminal narrowing of ≥50% in diameter for vessels ≥1.5 mm in diameter were considered significant stenosis and calculated by a computer program.[15] The scores were calculated based on angiographic findings by two operators who were blinded to other parameters. Average of the measurements were used for the analyses. To determine the interobserver variability, we performed reliability analysis. Reliability of the measurements was statistically very significant in respect to the Gensini scores (intraclass correlation coefficient of 0.906, $P < 0.001$) and to SYNTAX scores (intraclass correlation coefficient of 0.922, $P < 0.001$).

Statistical analysis

Analyses were performed using the SPSS 20.0 (SPSS, Inc., Chicago, Illinois). Continuous variables were defined as means and standard deviation; categorical variables were given as percentages. The Kolmogorov–Smirnov test was used to test the distribution pattern. The study population was assigned into tertiles based on RHR at admission. RHR was examined both as a continuous variable and as a categorical variable split at clinical cut points ≤70, 70–89, and ≥90 bpm. Comparisons of multiple mean values were carried out by the Kruskal–Wallis tests or analysis of variance as appropriate. Categorical variables were compared with the Chi-square test. Pearson correlation coefficient was computed to examine the association between two continuous variables. Multivariate analyses to seek for predictors of angiographic complexity expressed as Gensini and SYNTAX scores. A two-tailed $P < 0.05$ was considered significant.

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Results

This is a prospective, cross-sectional study. A total of 388 patients (283 male, 72.9%) were enrolled in the study. All patients had stable CAD and were undergone CAG. Patients were divided into three main groups, according to RHR. Group 1 composed of patients with RHR ≤70 (n = 217), group 2 composed of patients with RHR between 70 and 89 (n = 133), and group 3 composed of patients with RHR ≥90 bpm (n = 38). All patients had an average age of 61.3 ± 9.3 years, and the mean for RHR was 72.2 ± 11.7 bpm, with a range of 49–103 bpm. The mean RHR of groups were 63.4 ± 4.4 in group 1, 79.8 ± 5.1 in group 2, and 95.7 ± 3.4 in group 3 (P < 0.001). Mean Gensini score in all group population was 24.4 ± 22.5, and mean SYNTAX score was 13.6 ± 8.1 points. Table 1 shows the baseline characteristics of the study population as per RHR categories. There was no statistically significant difference in terms of age, sex, BMI, hyperlipidemia, left ventricular EF, glucose, creatinine, lipid profile, thyroid-stimulating hormone, and the prevalence of hypertension, DM, medications that affect heart rate and smoking habits among the three study groups.

Among hematological parameters, hemoglobin and platelet levels were similar between all three groups. However, white blood cell (WBC) was significantly higher in the group 3 than in the other two groups (P = 0.005 for both), whereas it was similar between the groups 1 and 2 (P = 0.829). C-reactive protein (CRP) was significantly higher in the group 3 compared to the other groups (P < 0.001), [Table 2].

In patients with CAD, Gensini score was strongly and positively correlated with CRP (r = 0.543; P < 0.001), RHR (r = 0.725; P < 0.001), and SYNTAX score (r = 0.680; P < 0.001), and negatively correlated with EF (r = −0.224; P < 0.001) and high-density lipoprotein (HDL) (r = −0.334; P < 0.001), [Table 3]. In addition, RHR was positively correlated with SYNTAX (r = 0.700; P < 0.001) and CRP (r = 0.754; P < 0.001) in patients.

Multivariate analyses were performed to seek for predictors of angiographic complexity expressed as Gensini and SYNTAX scores. Age, BMI, gender, RHR, CRP, and WBC count in the regression model [Table 4]. Only RHR was found to be statistically significant to predict angiographic complexity (for Gensini score β = 0.658, P < 0.001; for SYNTAX score β = 0.695, P < 0.001, respectively).

Discussion

The results of this study confirmed that the RHR tended to positively correlate with the severity of CAD. Furthermore, we demonstrated that the RHR was strongly associated with the severity and complexity of coronary atherosclerosis, independent of the age, BMI, DM, smoking, hypertension, and serum total cholesterol concentration. This finding showed the significant associations between RHR and the extent of CAD, which is compatible with previous studies.[16] Along with this, it has been reported that high RHR was related with an increased risk of hypertension,[17] type 2 diabetes,[18] dyslipidemia,[19] and metabolic syndrome.[20] Concurrently, it is clear that CAD takes role, at least partially in the translation of higher RHR correlated CAD complexity. RHR is an intriguing variable for risk stratification because it is a routinely collected, non-invasive vital sign that requires no special equipment for measurement. Therefore, this can produce novel implications about RHR in clinical and prognostic evaluations along with conventional risk factors.

Several studies have shown that high RHR is an independent risk factor for CV disease.[16–19] Diaz *et al*.[21] reported long-term data from 24,913 patients in the landmark

Table 1: Baseline descriptive characteristics of the study population

Variables	Total n=388	Group 1 n=217	Group 2 n=133	Group 3 n=38	P
Age (years)	61.3±9.3	60.7±9.6	61.6±9.4	63.4±6.9	0.134
Gender (male %)	283 (72.9)	150 (69.1)	104 (78.2)	29 (76.3)	0.159
BMI (kg/m^2)	24.6±3.0	24.5±3.2	24.8±2.5	24.4±3.1	0.195
Systolic BP (mmHg)	122.3±11.8	123.6±13.2	121.2±10.2	124.6±12.2	0.258
Diastolic BP (mmHg)	78.8±5.8	78.19±4.83	78.29±4.93	79.33±5.3	0.325
Antihypertensive (%)	161 (41.5)	98 (45.2)	49 (36.8)	14 (36.8)	0.256
Resting heart rate	72.2±11.77	63.4±4.4	79.8±5.1	95.7±3.4	**<0.001**
Hypertension (%)	238 (61.3)	131 (60.4)	82 (61.7)	25 (65.8)	0.815
Diabetes mellitus (%)	164 (42.3)	90 (41.5)	59 (44.4)	15 (39.5)	0.812
Current smoker (%)	174 (44.8)	100 (46.1)	56 (42.1)	18 (47.4)	0.728
Hyperlipidemia (%)	162 (41.7)	82 (42.6)	62 (45.4)	18 (47.4)	0.834
Family history (%)	155 (39.9)	84 (39.3)	55 (42.3)	16 (42.1)	0.767
LVEF (%)	60.3±9.4	60.2±5.6	60.6±8.4	59.4±4.8	0.337
The Syntax score	13.6±8.10	9.3±5.35	17.0±6.9	26.0±6.5	**<0.001**
The Gensini score	24.4±22.5	11.5±7.0	35.4±19.5	59.8±31.2	**<0.001**

BMI=Body mass index; LVEF=Left ventricular ejection fraction; Syntax=The Synergy between percutaneous coronary intervention with Taxus and cardiac surgery, Data are expressed as mean + SD and number (percentage)

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Table 2: Laboratory characteristics of the study population

	Total *n*=388	Group 1 *n*=217	Group 2 *n*=133	Group 3 *n*=38	*P*
Glucose (mg/dL)	123.98±52.43	120.24±46.13	129.07±61.42	128.19±53.03	0.498
Urea (mg/dL)	38.38±16.33	38.07±14.91	38.14±18.30	41.02±17.21	0.436
Creatinine (mg/dL)	0.92±0.24	0.94±0.26	0.89±0.21	0.92±0.24	0.352
Total cholesterol (mg/dL)	183.94±43.76	180.93±43.37	188.93±43.85	183.40±45.34	0.375
Triglyceride (mg/dL)	160.05±91.25	155.74±76.73	167.14±114.63	159.67±72.75	0.888
HDL cholesterol (mg/dL)	42.27±13.30	42.98±14.89	41.53±10.87	40.80±11.22	0.744
LDL cholesterol (mg/dL)	110.94±38.23	108.53±37.63	114.04±36.65	113.97±47.03	0.474
TSH (mU/L)	2.21±0.98	2.25±0.88	2.19±0.91	2.11±0.94	0.385
Hemoglobin (g/L)	14.03±2.69	14.10±2.66	14.19±2.81	13.07±2.22	0.067
Leukocyte ($\times10^9$/L)	8.05±2.05	7.79±2.07	8.45±2.06	8.15±1.62	**0.005**
Platelets ($\times10^9$/L)	259.33±68.58	258.43±62.80	261.21±73.52	257.89±83.22	0.841
CRP (mg/L)	3.42±1.25	2.69±0.63	4.12±0.96	5.11±1.73	**<0.001**

HDL=High-density lipoprotein; LDL=Low-density lipoprotein; TSH=Thyroid-stimulating hormone; CRP=C-reactive protein, Data are expressed as mean+SD

Table 3: Correlation of Gensini score with other study variables

	Gensini score	
	r	*P*
Age	0.090	0.077
BMI	0.045	0.373
Heart rate	0.725	**<0.001**
CRP	0.543	**<0.001**
HDL	−0.334	**<0.001**
LVEF	−0.224	**<0.001**
Syntax	0.680	**<0.001**

BMI=Body mass index; CRP=C-reactive protein; HDL=high-density lipoprotein; LVEF=Left ventricular ejection fraction; Syntax=The Synergy between percutaneous coronary intervention with Taxus and cardiac surgery

Table 4: Multvariate analyses of the variables in respect to Gensini (r^2=0.733, *P*<0.001) and SYNTAX scores (r^2=0.726, *P*<0.001)

	Gensini score		SYNTAX score	
	β	*P*	β	*P*
Age (year)	0.031	0.380	−0.005	0.884
BMI (kg/m^2)	−0.039	0.264	0.028	0.433
Gender	−0.030	0.400	−0.016	0.662
Resting heart rate (bpm)	0.658	<0.001	0.695	<0.001
CRP (mg/L)	0.093	0.079	0.040	0.453
WBC count ($\times10^9$/L)	−0.047	0.190	−0.038	0.292

BMI=Body mass index; CRP=C-reactive protein; WBC=White blood cell

Coronary Artery Surgery Study registry median follow up of 14.7 years. High RHR was related to higher rates of all-cause mortality and CV mortality. Multivariate analysis revealed that patients with a RHR of >83 bpm, compared with <62 bpm, were associated with 32% increase in total mortality and 31% increase in CV mortality even after adjustment for multiple potentially confounding clinical variables. Lonn *et al*.[22] showed the relationship between RHR and CV mortality from a population of 31,531 with stable CAD that the highest (>78 bpm) versus lowest (<58 bpm) mean RHR quintile was associated with a 77% increase in CV mortality and 65% increase in all-cause mortality. Kolloch *et al*.[23] found that if antihypertensive agents (verapamil or atenolol) that lower RHR were used in hypertensive patients, there was a significant decrease in CAD risk compared to others. Higher baseline and follow-up RHR were associated with increased adverse outcome risks, with a linear relationship for baseline RHR and J-shaped relationship for follow-up RHR. Although follow-up RHR was independently associated with adverse outcomes, it added less excess risk than baseline conditions such as heart failure and diabetes. The atenolol strategy reduced RHR more than verapamil ($P < 0.001$), yet adverse outcomes were similar ($P = 0.62$). Therefore, in our study, patients who used drugs that affect heart rate were excluded from the study, and incorrect results were avoided.

RHR is determined by sinus node, which is mostly controlled by the combination of sympathetic and vagal activities. Hence, an elevated RHR may show sympathovagal imbalance stemming either from sympathetic overactivity or a decrease in vagal activity. Heart rate is the most fundamental determinant of myocardial oxygen perfusion. Myocardial ischemia may develop due to an increase in myocardial oxygen consumption or decreased diastolic filling time.[24] Elevated RHR is related to arterial stiffness and with abnormal patterns of endothelial shear stress. Long-lasting high RHR can lead to arterial wall remodelling and a structural increase in stiffness. Our study measured heart rate at rest, and the estimated relationship with the severity and complexity of coronary atherosclerosisis likely to represent a chronic effect.

We found an increase in CRP levels parallel to RHR and the Gensini score. These findings support that high RHR may also be a sign of increased inflammation, and heart rate is not the single reason for an increased Gensini score. CRP is a marker of inflammation that is frequently used in clinical practice. Inflammation plays an important role in all stages of

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atherosclerosis.[25] Serum CRP, an acute phase protein from the liver, increases as a response to inflammation and can promote risk prediction for patients with CAD. Furthermore, high CRP levels were reported to be associated with the extent of CAD in patients with stable CAD. Sympathovagal imbalance may also be related with inflammation and therefore it may be possible to lead atherosclerosis.[24,25]

There are some limitations in the present study. Firstly, it is a single-center, retrospective study with no follow up. Therefore, the results of this study could, to some extent, represent the relationship between RHR and the severity of CAD. Secondly, our study population was relatively small because of our exclusion criteria.

Conclusions

In our study, RHR was positively associated with CRP, Gensini and SYNTAX scores. RHR is an effective easily available marker for the assessment of severity of CAD and helps in risk stratification of CAD patients. However, further prospective and multicenter clinical studies are needed to verify these findings.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Hennekens CH. Increasing burden of cardiovascular disease: Current knowledge and future directions for research on risk factors. Circulation 1998;97:1095-102.
2. Fujiura Y, Adachi H, Tsuruta M, Jacobs DR, Hirai Y, Imaizumi T. Heart rate and mortality in a Japanese general population: An 18-year follow-up study. J Clin Epidemiol 2001;54:495-500.
3. Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a French population role of age, gender, and blood pressure. Hypertension 1999;33:44-52.
4. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010;159:612-9.
5. Kannel WB. Range of serum cholesterol values in the poulation developing coronary artery disease. Am J Cardiol 1995;76:69-77.
6. Bagheri B, Meshkini F, Dinarvand K, Alikhani Z, Haysom M, Rasouli M. Life psychosocial stresses and coronary artery disease. Int J Prev Med 2016;7:106.
7. Jahangiry L, Najafi M, Farhangi MA, Jafarabadi MA. Coronary artery bypass graft surgery outcomes following 6.5 years: A nested case-control study. Int J Prev Med 2017;8:23.
8. Palatini P. Heart Rate: A strong predictor of mortality in subjects with coronary artery disease. Eur Heart J 2005;26:943-5.
9. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, Investigators B. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A randomised, doubleblind, placebo-controlled trial. Lancet 2008;372:807-16.
10. Gensini G. A more meaningful scoring system for determin-ing the severity of coronary artery disease. Am J Cardiol 1983;51:606.
11. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J 1983;51:606.
12. Sianos G, Morel M-A, Kappetein AP, Morice MC, Colombo A, Dawkins K, *et al*. The SYNTAX Score: An angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219-27.
13. Hozawa A, Ohkubo T, Kikuya M, Ugajin T, Yamaguchi J, Asayama K, *et al*. Prognostic value of home heart rate for cardiovascular mortality in the general population: The Ohasama study. Am J Hypertens 2004;17:1005-10.
14. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51 (4 Suppl):5-40.
15. SYNTAX score. Available from: http://www.SYNTAXscore.com. [Last accessed on 2018 May 18].
16. Yilmaz S, Sen F, Akboga MK, Balci KG, Aras D, Temizhan A, *et al*. The relationship between resting heart rate and SYNTAX score in patients with stable coronary artery disease. Angiology 2017;68:168-73.
17. Wang , Liu X, Guo X, Dong Y, Wu Y, Huang Z, *et al*. Resting heart rate and risk of hypertension: Results of the Kailuan cohort study. J. Hypertens 2014;32:1600-5.
18. Aune D, Ó Hartaigh B, Vatten LJ. Vatten, resting heart rate and the risk of type 2 diabetes: A systematic review and dose–response meta-analysis of cohort studies. Nutr Metab Cardiovasc Dis 2015;25:526-34.
19. Sun JC, Huang XL, Deng XR, Lv XF, Lu JL, Chen YH, *et al*. Elevated resting heart rate is associated with dyslipidemia in middle-aged and elderly Chinese. Biomed Environ Sci 2014;27:601-5.
20. Zhang X, Li Y, Wang F, Zang J, Liu X, Zhang H, *et al*. Independent and combined effects of resting heart rate and pulse pressure with metabolic syndrome in Chinese rural population: The Henan Rural Cohort study. Clin Chim Acta 2018;484:246-52.
21. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005;26:967-74.
22. Lonn EM, Rambihar S, Gao P, Custodis FF, Sliwa K, Teo KK, *et al*. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: An analysis of ONTARGET/TRANSCEND. Clin Res Cardiol 2014;103:149-59.
23. Kolloch R, Legler UF, Champion A, Cooper-Dehoff RM, Handberg E, Zhou Q, *et al*. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: Findings from the International VerapamilSR/trandolapril Study (INVEST). Eur Heart J 2008;29:1327-34.
24. Menown IB, Davies S, Gupta S, Kalra PR, Lang CC, Morley C, *et al*. Resting heart rate and outcomes in patients with cardiovascular disease: Where do we currently stand? Cardiovasc Ther 2013;31:215-23.
25. Drakopoulou M, Toutouzas K, Stefanadi E, Tsiamis E, Tousoulis D, Stefanadis C. Association of inflammatory markers with angiographic severity and extent of coronary artery disease. Atherosclerosis 2009;206:335-9.