Journal of Clinical & Experimental Cardiology

Hamdy et al., J Clin Exp Cardiolog 2015, 6:12
DOI: 10.4172/2155-9880.1000413

Case Report Open Access

Can Early 24 Hours Holter Monitoring Predict Obstructive Coronary Artery Lesions in Patients with Low Risk Acute Coronary Syndrome?

Hamdy A[1], **Taha TTI**[2*], **Saad M**[1] **and Nageeb W**[1]

[1]*Cardiology Department, Al-Minia University Hospital, Egypt*

[2]*Cardiology and Coronary Care Department, Faculty of Medicine, Al-Minia University, Egypt*

[*]**Corresponding author:** Taha TTI, Cardiology and Coronary Care Department, Faculty of Medicine, Al-Minia University, Egypt, Tel: 00971529853949; E-mail: Tamertaha76@gmail.com

Received date: Oct 16, 2015; **Accepted date:** Nov 25, 2015; **Published date:** Nov 28, 2015

Introduction

Identification of patients at increased risk for death due to acute coronary syndrome (ACS) can add in risk stratification and guide the next step in the management of those patients.

Easy, Safe and cost-effective available tools to aid in risk assessment are needed. Heart rate variability (HRV) is noninvasive cardiac monitoring that reflects autonomic cardiac function and may provide insight into patients' ability to recover from physiological insult, such as myocardial infarction (MI) or an episode of UA [1,2].

Phasic differences in the intervals between normal to normal heart beats often referred to as heart rate variability (HRV) are known to be reliable measures of autonomic control of the heart. In various pathological conditions such as diabetic neuropathy, heart failure, coronary heart disease (CHD), and essential hypertension a marked decrease in HRV has been found. Studies on normal populations suggest that decreased HRV is also a significant, independent risk factor for mortality and incident coronary events [3].

Autonomic nervous system dysfunction and clinical depression have been associated with a significant risk of adverse CV outcomes in ACS patients. Cardiac autonomic physiology, as measured by heart rate variability (HRV), appears to have a complex interplay with psychosocial factors.

In a 1987 study by Kleiger et al, the standard devia-tion of normal sinus RR intervals (SDNN), measured using 24-hour Holter recordings, was associated with all-cause death in the post-MI population [4].

Subsequent research has supported the association of decreased HRV and mortality in patients with cardiovascular disease. However, the prognostic value of HRV measurement initiated within the first hour of ED presentation during the earliest phases of ACS need to be studied for care plan [1].

The primary aims of this study were to answer the following questions in patients presenting with acute coronary syndrome:

1. Is HRV measured during the 24 hours from the onset of chest pain can predict the result of stress test and significant coronary obstruction lesions in those patients. 2. Which HRV variables, if any, may serve as clinically useful tools to aid in immediate risk stratification for ACS patients?

Patients & Methods

This prospective study was conducted at the Cardiology department of Minia University hospital during the period from May 2014 to May 2015.

The current study included 100 patients who presented at our department complaining of typical angina pain and having no objective evidence on cardiac ischemia e.g. non diagnostic ECG and negative cardiac biomarker.

Written consent was obtained at the time of recruitment.

All patients were subjected to:

Thorough history taking and clinical examination.

Laboratory Investigation: fasting blood sugar, serum creatinine and serum troponin.

Heart Rate Variability Analysis.

We placed 24-hour Holter recorders (Cardio Holter TM, Nasiff Associates Cardio Card TM, USA) as soon as possible after the patients arrived in the cardiology department. Trained research nurses applied the ECG leads, supervised monitoring, and downloaded data to the review station.

All recordings were also examined visually and artifacts were deleted manually. All of the recordings had at least 22 hours of data once the artifacts were deleted. HRV parameters were calculated and statistically analyzed. Both the time- and frequency domain parameters of HRV were determined through analysis of the entire 24 hours recordings. Time-domain HRV parameters used in this study were chosen according to the guidelines of the European Society of Cardiology and the North American Society of Pacemaker and Electrophysiology, and included mean RR intervals (RR), percentage of differences between adjacent NN intervals that are >50 msec (pNN50), standard deviation of all normal RR intervals (SDNN), standard deviation of the mean of normal RR intervals at each 5 minute segment (SDANN), and root mean squared of successive RR intervals (RMSSD) [3]. Frequency-domain HRV parameters used in this study were chosen according to the same guidelines, and included variance of all NN intervals (total power: approximately 0.4 Hz), power in the very low frequency range (VLF: 0.003-0.04 Hz), power in the low frequency range (LF: 0.04-0.15 Hz), and power in the high frequency range (HF: 0.15-0.4 Hz) [3]. All recordings were made under similar conditions and in a similar environment.

4. Exercise Stress Test

Treadmill exercise tests (T2100 GE stress ECG system) were performed to all patients using the Bruce protocol.

ST segment depression was defined vas 0.1 mV or greater horizontal or down sloping ST segment depression at 80 msec after the J point and Duke Score was calculated. The equation for calculating the Duke treadmill score (DTS) is DTS=exercise time-(5 × ST deviation)-(4 × exercise angina), with 0=no chest pain, 1=none limiting chest pain, and 2=exercise-limiting chest pain [5].

5. Coronary angiography:

Elective diagnostic coronary angiography (Inova 2000 GE, USA) was performed only to patients with abnormal stress test.

Coronary angiograms were evaluated to assess the abnormality. Obstructive coronary artery disease was defined as stenosis that obstructs 50% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter. Coronary ectasia was defined as dilatation of an arterial segment to a diameter at least 1.5 times that of the adjacent normal coronary artery [6].

Statistical Analysis

Statistical analysis was performed using commercial software (SPSS 19.0, Chicago, IL, USA; Med Calc 11.3, Maria kerke, Belgium). For normally distributed variables, mean and ± SD are listed. Otherwise, median values are given. deference in variables among the groups were assessed using either an one-way ANOVA or Kruskal-Wallis analysis of variance, with multiple comparisons made using Bonferroni's test in case of global statistical significance (as indicated), whereas proportions were compared using chi-square test. Multivariate analysis of covariance (MANCOVA) was used to compare the HRV and HRT parameters among groups; age, systolic and diastolic blood pressures, body mass index, hemoglobin, and serum creatinine clearance were accepted as covariates. Correlations were determined using Spearman's test. A receiver operating characteristic (ROC) curve was constructed for HRV and HRT parameters to test the electiveness of various cut of points in predicting obstructive and non-obstructive CAD. The area under the ROC curve and the sensitivity and specificity of the most appropriate cut of points of HRV and HRT parameters for predicting CAD was calculated. p values below 0.05 were considered statistically significant.

Results

The current study included 100 patients who attending our department complaining of typical angina pain and having no objective evidence on cardiac ischemia e.g. non diagnostic ECG and negative cardiac biomarker.

Treadmill stress test was performed to all patients; patients were classified according to stress test results into two groups:

Group I: included 42 patients who had a normal stress test. The main age of this group was 50 ± 8.8 (ranged from 39-70).

Group II: included 58 Patients who had an abnormal stress test either Positive in 45 patients or Equivocal in 13 patients. The main age of this group was 54.66 ± 7.6 (ranged from 40-67).

There was statically significant difference regarding the mean age among the studied groups (p=0.006). While there was no significant difference between both groups regarding other parameters as seen in (Table 1).

	Negative stress test	Positive stress test	Significant level
Age	50 ± 8.8	54.66 ± 7.6	0.006
Sex	17 males, 25 females	34 males, 24 females	0.1
Smoking	2	7	0.4
Weight	77.7 ± 7.5	79.1 ± 6.9	0.3
Systolic BP	131.1 ± 17	135 ± 19	0.289
Diastolic BP	82.5 ± 9.7	86.8 ± 9.5	0.485
Random blood sugar	130.4 ± 65	129.8 ± 63.3	0.964
GFR	100.69 ± 33.07	108.36 ± 39.95	0.3
ALT	26.2 ± 8	25.6 ± 8.14	0.7
AST	26.26 ± 7.4	26.5 ± 6.5	0.8

Table 1: Demographic and Laboratory Features Of Both Main Groups. *BP: Blood pressure, GFR: Glomerular filtration rate, ALT: Alanine transaminase, AST: Aspartate Transaminase.

Echocardiogram was performed in all patients. All patients had normal LV systolic function. The number of patients with resting regional wall motion was significantly more in group II in comparison to group I (p=0.07).There was no statistically significant difference regarding presence of diastolic dysfunction among main two groups p=0.6) (Table 2).

	Group I	Group II	Significant level
DD*	15	11	0.63
EF	62.2 ± 6.49	61.6 ± 6	0.744
Presence of RWMA	1	12	0.07

Table 2: Echocardiographic features of both groups.

	Group I	Group II	Significant level
SDANN	35.8 ± 28.3	42.57 ± 41.8	36
SDNN	127.35 ± 24.5	101.96 ± 30.65	0.0001*
SDNN INDEX	101.5 ± 67.8	113.4 ± 75	0.42
pNN50	13.94 ± 7.8	15.01 ± 11.5	0.6
RMSSD	89.23 ± 29.7	84.1 ± 35.64	0.4
VLF	1107.5 ± 487	1298.38 ± 787.2	0.16
LF	999.2 ± 191.3	959.7 ± 350.9	0.5
HF	951.1 ± 313.25	937.58 ± 441.7	0.8

Table 3: Heart Rate Variability parameters in both groups

Comparison between Heart rate variability indices and stress test results:

The mean SDNN was statistically significantly lower in group II when compared to group I (p=0.0001). However, the rest of the parameters were not significantly different among both groups. (Table 3). Coronary angiography was performed in patients of group II. Accordingly those patients further classified into three subgroups (Figure 1):

Subgroup IIA: included18 patients who had angiographically normal coronary artery.

Subgroup IIB: included 12 patients who had one or more ectatic segments (Non obstructive CAD).

Subgroup IIC: included 28 patients who had obstructive CAD.

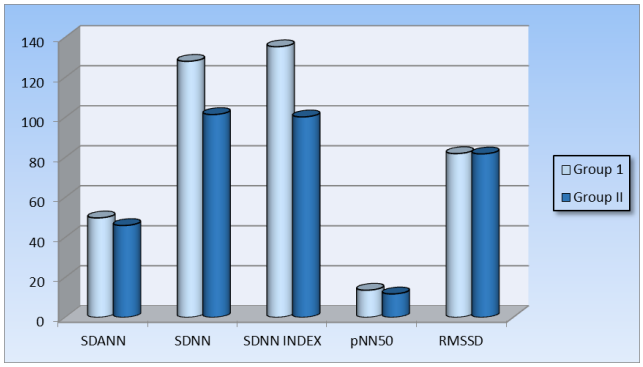

Figure 1: Comparison between Time Domain HRV in the studied groups

No statistically significant difference regarding the mean age, sex, the number of smoking patients or, patients weight among three subgroups. (Table 4)

	(Subgroup IIA)	(Subgroup IIB)	(Subgroup IIC)	Significant level
Age	53 ± 7.5	54.08 ± 5.9	55.96 ± 8.2	NS
Sex	9 M , 9 F	6F, 6M	9 F, 19M	NS
Smoking	0	1	6	NS
Weight	78 ± 6.4	78.66 ± 6.05	80.10 ± 7.6	NS
Systolic BP	127.77 ± 12.15	139.16 ± 29.06	138.2 ± 16.78	NS
Diastolic BP	82.2 ± 5.4	84.16 ± 11.6	85.71 ± 11.68	NS
Random blood sugar	120 ± 73	121.85 ± 40	139.6 ± 65	NS
GFR	105.14 ± 42.3	118.3 ± 22.6	106.72 ± 44.6	NS
ALT	23.55 ± 6.4	22.9 ± 7.4	28.07 ± 8.9	NS
AST	23.5 ± 3.86	27.16 ± 8.2	28.21 ± 6.5	NS

Table 4: Demographic and Laboratory Features Between Subgroups

Comparison between Heart rate variability indices and coronary angiography results:

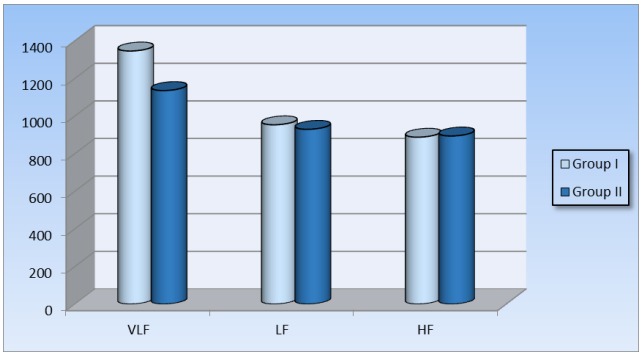

Figure 2: Comparison between Frequency Domain HRV in the studied groups.

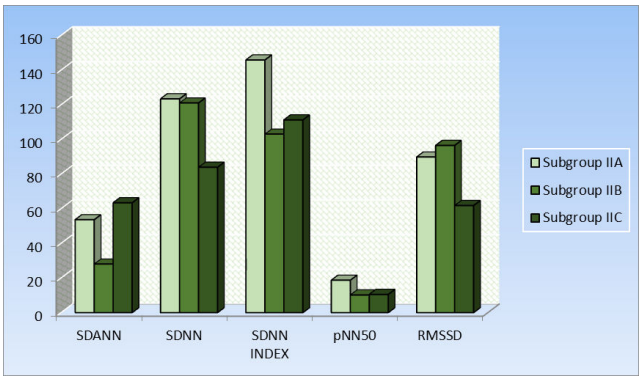

Figure 3: Comparison between the Studied Subgroups as Regard Time Domain HRV

Subgroup IIA	Subgroup IIB	Subgroup IIC	Significant level	
SDANN	49.8 ± 37	28.25 ± 1.138	44.05 ± 51	0.378
SDNN	123.2 ± 21	118.3 ± 24.6	81.3 ± 24.1	0.0001
SDNN INDEX	153.2 ± 90	81.6 ± 79	101.36 ± 52.54	0.18
PNN50	24.37 ± 15.1	12.5 ± 6.08	10.06 ± 5.8	0.0001
RMSSD	103.4 ± 35.1	110.25 ± 26.56	60.48 ± 22.08	0.0001
VLF	1671.88 ± 1174	1008.16 ± 98.5	1182.66 ± 539	0.04
LF	1127.2 ± 412.5	1060 ± 138	809.12 ± 313.53	0.004
HF	1076.13 ± 538	1163.16 ± 377	751.82 ± 316.4	0.005

Table 5: Heart Rate Variability Parameters in the Subgroups

While other time domain heart rate variability parameters had no statistically significance difference between the 3 subgroups as seen in Table 5. The mean SDNN was 123.2 ± 21 (ranged from 106-196) in subgroup IIA versus 118.3 ± 24.6 (ranged from 93-182) in subgroup

IIB and 81.3 ± 24.1 (ranged from 31-129) in subgroup IIC, which was statistically significantly lower in subgroup IIC (p=0.0001). The mean pNN50 was 24.37 ± 15.1 (ranged from 1-45) in subgroup IIA versus 12.5 ± 6.08 (ranged from 2-24) in subgroup IIB and 10.06 ± 5.8 (ranged from 1-23) in subgroup IIC, which was statically significantly lower in subgroup IIC (p=0.0001). The mean RMSSD was 103.4 ± 35.1 (ranged from 16-139) in subgroup IIA versus 110.25 ± 26.56 (ranged from 69-152) in subgroup IIB and 60.48 ± 22.08 (ranged from 35-127) in subgroup IIC, Which was statically significantly lower in subgroup IIC p=0.0001). (Figure 3, Table 5).

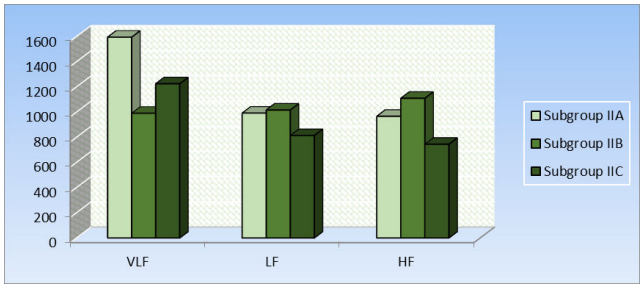

Figure 4: Comparison between the Studied Groups as Regard Frequency Domain HRV

	Stress Test	
	r	p
SDANN	0.205	0.041
SDNN	-0.407	<0.001
SDNN INDEX	0.02	0.843
pNN50	-0.038	0.705
RMSSD	-0.088	0.381
VLF	0.185	0.065
LF	0.004	0.972
HF	-0.046	0.652

Table 6: Correlation of HRV Indices with Positive Stress Test

The mean VLF was 1671.88 ± 1174 (ranged from 712-5533) in subgroup IIA versus 1008.16 ± 98.5 (ranged from 797-1190) in subgroup IIB and 1182.66 ± 539 (ranged from 247-3033) in subgroup IIC, Which was statically significantly lower in subgroup IIC (p=0.04). The mean LF was 1127.2 ± 412.5 (ranged from 95-1805) in subgroup IIA versus 1060 ± 138 (ranged from 722-1220) in subgroup IIB and 809.12 ± 313.53 (ranged from 196-1163) in subgroup IIC, Which was statically significantly lower in subgroup IIC (p=0.004). The mean HF was 1076.13 ± 538 (ranged from 26-2098) in subgroup IIA versus 1163.16 ± 377 (ranged from 616-1901) in subgroup IIB and 751.82 ± 316.4 (ranged from 154-1142) in subgroup IIC, which was statistically significantly lower in subgroup IIC (p=0.005). (Figure 4, Table 5)

Correlations between heart rate variability indices and stress test:

SDNN showed a significant negative correlation with positive stress test (p=<0.001).

SDANN showed a significant positive correlation with positive stress test (p=0.041), while other parameters showed no statistically significant correlation. (Table 6)

Correlation between heart rate variability indices and obstructive CAD:

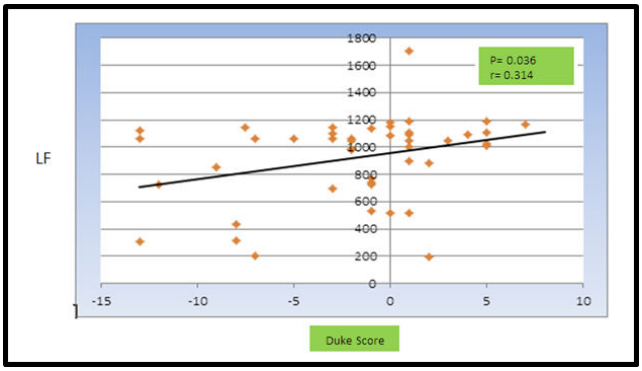

Figure 5: Correlation of LF with Duke Score.

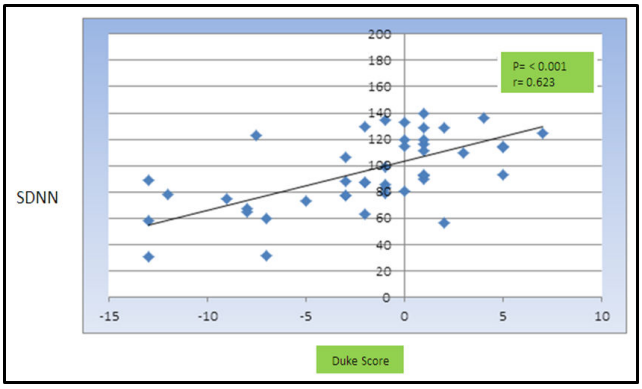

Figure 6: Correlation of SDNN with Duke Score.

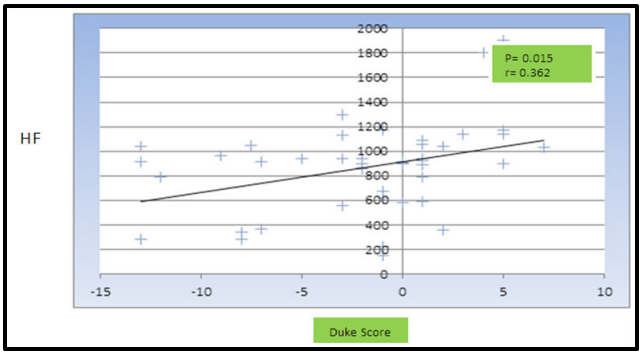

Figure 7: Correlation of HF with Duke Score.

SDNN, RMSSD, LF showed a highly significant negative correlation with obstructive CAD (p= <0.001). (Figure 8)

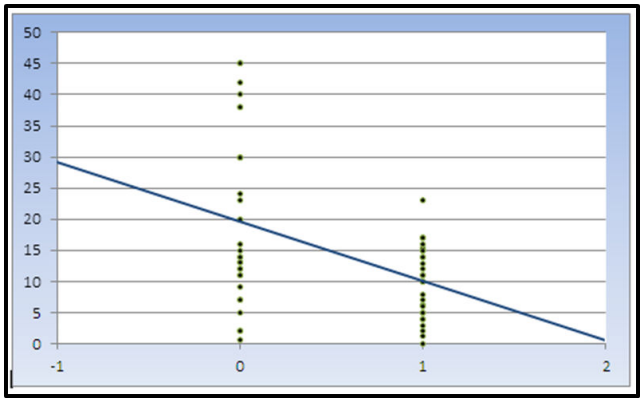

Figure 8: Correlation Of pNN50 with Obstructive CAD.

Also pNN50 and HF showed a significant negative correlation with obstructive CAD (P=0.007). (Figure 9)

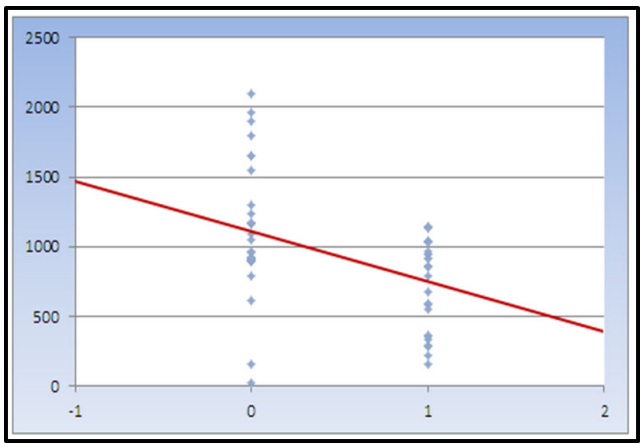

Figure 9: Correlation of HF with Obstructive CAD.

SDANN, SDNN INDEX and VLF showed no significant correlation with obstructive CAD.

Discussion

A substantial proportion of patients presenting to the emergency department (ED) with acute chest discomfort have normal electrocardiograms (ECGs) and initially reassuring conventional cardiac troponin concentrations, but still subsequently develop myocardial infarction [7]. So the goal and greatest challenges are the integration of multiple techniques and tests into clinical practice in a logical and cost-effective strategy to answer the following questions, Does this patient have ACS or can he or she be discharged immediately? Should this patient undergo early catheterization? What is this patient's risk?

The prognostic significance of HRV has been extensively studied in different populations especially in patient who survived an AMI. SDNN is a universally recognized parameter with the highest specificity and sensitivity as compared with other lethal outcomes predictors [8-10].

Several studies demonstrated that reduced heart variability can be clinically relevant in the diagnostic evaluation of the coronary artery disease [11,12].

This study aimed to create a non-invasive, economical and risk-free method in clinical evaluation and diagnosis of significant CAD among patients with unstable angina.

In the present study, we demonstrated:

The relationship between heart rate variability indices and stress test results in patient diagnosed clinically as low risk acute coronary syndrome.

The relationship between heart rate variability indices and diagnosis of obstructive CAD.

As a main finding, HRV indices were significantly reduced in patient with obstructive CAD.

Reduced HRV indices have a significant negative correlation with obstructive CAD.

A lot of previous studies showed the relation between HRV and presence of CAD, but the results was controversial according to the population who had been investigated.

Previous studies support our findings like Trigulova and Kurbanov, 2011 found that ECG Holter monitoring started in patients with unstable angina pectoris within first 24 hours after the last pain attack demonstrated all HRV time parameters confidently lower than those in healthy subjects of the same age [13] But analysis of ECG Holter monitoring parameters detected no informative HRV markers to predict either adverse or favorable IHD course.

Also Huang et al, 1995 all measures of HRV were reduced in patients with acute coronary syndrome compared to normal controls ($p<0.001$) while there were no significant difference in measures of HRV between unstable angina and myocardial infarction patients.(14) In patients with unstable angina who stabilized after admission, HRV had increased by the second 24 hours of monitoring.

In another study done by Goldkorn et al, 2015 who used HRV as a screening tool for detection of myocardial ischemia in patient without known CAD found that reduced HRV indices were highly correlated with the presence of significant CAD ($p=<0.001$) in patients who underwent coronary angiography during follow-up [15]

Celik et al, 2011 used HRV to discriminate true CAD in patients with ST segment depression without angina during exercise stress testing. (16) They showed that HRV and HRT parameters are blunted in patients with CAD and that is even more pronounced in those with obstructive CAD. SDNN, LF, pNN50, RMSSD, total power, and HF was significantly lower in patients with obstructive CAD ($p<0.001$).They recommend that SDNN ≤ 69.63 msec had high diagnostic accuracy for predicting obstructive CAD while SDNN ≤ 75.84 msec and LF ≤ 943 msec had significant diagnostic accuracy for predicting non-obstructive CAD.

Pivatell et al 2012 showed that patients with stable angina had significantly reduced HRV indices, especially SDNN ($p=0.0209$), RMSSD ($p=0.03$), NN50 ($p=0.04$) and HF ($p=0.007$), in patient with obstructive CAD [17].

Takei et al. 2007 found that among ACS patients; all indicators of HRV in multi-vessels diseased group were lower significantly than single vessel diseased; same finding by Hayano et al 1990 [12,18].

Tamoši et al 2005 showed that the value of HRV during deep breathing test was found to be lower in patients with coronary artery stenosis ≥ 50% comparing to patients with stenosis ≥ 30% (p=0.02) which showed diminished vagal cardiac activity in patients with CAD [19]. They also found that liability of variability during deep breathing was expressed most in the myocardial infarction patients who is expected to have the highest lesions.

Inspecting these studies revealed that they support our finding that patients of obstructive CAD had reduced heart rate variability indices.

In disagreement with our finding, Wennerblom et al 2000 showed that patient with uncomplicated CAD and no previous myocardial infarction had reduced HRV mainly affecting the high and low frequencies [20]. They also suggest that the small number of patient in their study is the probable reason for the fact that the SDNN and SDANN reduction in the angina patient was non-significant.

Lanza et al collected data from 1997-2001 using Holter recordings that were started within 24 hours of hospital admission in 543 UA patients [21]. Primary endpoints were in-hospital and 6-month deaths, and a secondary endpoint was nonfatal acute MI. the SDNN index and LF power were significantly associated with in-hospital mortality in multivariate analysis, while other parameters shows no statistically significance.

Interestingly, alteration of RMSSD related to parasympathetic nerve in HRV is not identical in different studies which means that there is no clear correlation between RMSSD and severity of CAD [18,21,22].

The mechanism of low heart rate variability in patient with CAD is not exactly known but previous studies found that HRV can be used as a predictor for progression of atherosclerosis [23].

At last, HRV measured close to the ACS onset may assist in risk stratification. HRV cut-points may provide additional, incremental prognostic information to established assessment guidelines, and may be worthy of additional study [24].

Practice standards recommend 24 hours of cardiac monitoring for ACS patients after ED presentation. Our Holter findings suggest that use of HRV measurements to assist in identifying patients at highest risk for adverse events might be a practical addition to continuous ECG monitoring.

HRV represent a non-invasive bedside test that could be incorporated into heart rate monitoring devices already present in ambulances and emergency departments.

Our study had some limitations. First, long term follow up of the adverse cardio-vascular outcome for these patients needed to be studied. However, this would need a larger scale study which a larger sample of patients and longer duration of follow up which is beyond the scope of our study. Second, recent ESC guidelines recommended the assessment of serum copoptien level if the first two troponin measurements are not conclusive and the clinical condition is still suggestive of ACS [25]. However, these recommendations were published after finishing our work, so we were unable to evaluate this test. Finally, the effect of drug therapy was not included in that work. Similar to long term adverse cardio-vascular outcome, this needs large scale studies to produce conclusive results.

References

1. Harris PR, Stein PK, Fung GL, Drew BJ (2014) Heart rate variability measured early in patients with evolving acute coronary syndrome and 1-year outcomes of rehospitalization and mortality. Vasc Health Risk Manag 10: 451-464.
2. Lahiri MK, Kannankeril PJ, Goldberger JJ (2008) Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. J Am Coll Cardiol 51: 1725-1733.
3. Janszky, M. Ericson, M. A. Mittleman, S. Wamala, F. Al-Khalil, et al. (2004) Heart rate variability in long-term risk assessment in middle aged women with coronary heart disease: The Stockholm Female Coronary Risk Stud. J Intern Med 255: 13-21.
4. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59: 256-262.
5. Malik M (1996) Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 17: 354-381.
6. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, et al. (1987) Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 106: 793-800.
7. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, et al. (2000) Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 342: 1163-1170.
8. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59: 256-262.
9. La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ (1998) Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes after Myocardial Infarction) Investigators. Lancet 351: 478-484.
10. Erdogan A, Coch M, Bilgin M, Parahuleva M, Tillmanns H, et al. (2008) "Prognostic value of heart rate variability after acute myocardial infarction in the era of immediate reperfusion." Herzschrittmacherther Elektrophysiol 19: 161-168.
11. Rich MW, Saini JS, Kleiger RE, Carney RM, teVelde A, et al. (1988) Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. Am J Cardiol 62: 714-717.
12. Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, et al. (1990) Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. Circulation 81: 1217-1224.
13. Trigulova RK, Kurbanov RD (2011) Heart Rate Variability as a Predictor of Adverse Prognosis in Patients with Unstable Angina Pectoris and Concomitant Diabetes Mellitus. International Journal of Applied and Fundamental Research 6: 22-25.
14. Huang J1, Sopher SM, Leatham E, Redwood S, Camm AJ, et al. (1995) Heart rate variability depression in patients with unstable angina. Am Heart J 130: 772-779.
15. Goldkorn R, Naimushin A, Shlomo N, Dan A, Oieru D, et al. (2015) Comparison of the Usefulness of Heart Rate Variability Versus Exercise Stress Testing for the Detection of Myocardial Ischemia in Patients Without Known Coronary Artery Disease. The American Journal of Cardiology 115: 1518-1522.
16. Celik A, Ozturk A, Ozbek K, Kadi H, Koc F et al. "Heart Rate Variability and Turbulence to Determine True Coronary Artery Disease in Patients with ST Segment Depression Without Angina During Exercise Stress Testing." Clin Invest Med 34: E349.
17. Pivatelli FC, Dos Santos MA, Fernandes GB, Gatti M, de Abreu LC et al. (2012) Sensitivity, specificity and predictive values of linear and nonlinear indices of heart rate variability in stable angina patients. Int Arch Med 5: 31.

18. Takei Y, Tomiyama H, Tanaka N, Yamashina A (2007) Close relationship between sympathetic activation and coronary microvascular dysfunction during acute hyperglycemia in subjects with atherosclerotic risk factors. Circ J 71: 202-206.
19. Tamoši M, Urbonavi G, Vainoras A, Gargasas G, Kaminskienė S et al. (2005) Influence of Deep Breathing on Heart Rate Variability in Patients with Ischemic Heart Disease 3: 3.
20. Wennerblom B, Lurje L, Tygesen, Vahisalo R, Hjalmarson A (2000) Patients with uncomplicated coronary artery disease have reduced heart rate variability mainly affecting vagal tone. Heart 83: 290-294.
21. Lanza GA, Cianflone D, Rebuzzi AG, Angeloni G, Sestito A, et al. (2006) Prognostic value of ventricular arrhythmias and heart rate variability in patients with unstable angina. Heart 92: 1055-1063.
22. Feng J, Wang A, Gao C, Zhang J, Chen Z, et al. (2015) Altered heart rate variability depend on the characteristics of coronary lesions in stable angina pectoris. Anatol J Cardiol 15: 496-501.
23. Huikuri HV, Jokinen V, Syvänne M, Nieminen MS, Airaksinen KE, et al. (1999) Heart rate variability and progression of coronary atherosclerosis. Arterioscler Thromb Vasc Biol 19: 1979-1985.
24. Harris PR, Stein PK, Fung GL, Drew BJ (2014) Heart rate variability measured early in patients with evolving acute coronary syndrome and 1-year outcomes of rehospitalization and mortality. Vasc Health Risk Manag 10: 451-464.
25. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, et al. (2015) "2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation." European Heart Journal.