Original research article

Assessment of Autonomic Function in Patients with Coronary Artery Disease

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Abstract

Background: Cardiovascular diseases are a major cause of mortality and morbidity. Early detection of cardiovascular disease will help to effectively treat the disease and avoid complications. There is an adverse impact on autonomics functions in coronary artery disease (CAD) resulting in sympathetic predominance. Heart rate variability (HRV) is a non-invasive economical tool to assess the autonomic function.

Material and methods: The study was conducted in the Department of Cardiology, AIIMS, New Delhi. Thirty patients with TMT positive/angiographically proven CAD admitted for elective Percutaneous Transluminal Coronary Angioplasty (PTCA) satisfying the inclusion and exclusion criteria in the age group of 40 to 65 years served as cases. The control group consisted of age, anthropometrically matched and TMT negative subjects who satisfied the inclusion and exclusion criteria.

Conclusion: Our study shows that the patients with CAD had a reduced HRV. In patients with CAD, there was an increase in sympathetic activity and reduced parasympathetic activity. There was improvement in HRV on third day following PTCA indicating a better prognosis.

Keywords – Heart rate variability, percutaneous transluminal coronary angioplasty, parasympathetic predominance.

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality in the developing and the developed countries. In India, mortality attributable to cardiovascular disease is expected to rise by 103% in men and by 90% in women from 1985 to 2015. Importantly, the age of onset of disease has been decreasing. Thus, research to identify potential risk factors causing CAD is of great importance. Early identification of risk factors can be used to prevent the complications of CAD by suitable lifestyle modifications. A cost-effective preventive strategy needs to focus on reducing risk factors both in the individual and in the population at large. However, a key factor that hampers the development of such preventive strategies in developing countries such as India is the meager amount (8%) of published literature on CAD research available from these countries. Much of the knowledge of risk factors for CAD has been acquired from studies

conducted in the Western population. It is widely believed that the association of these risk factors with CAD in other populations needsto be ascertained, and there is speculation that differences might range from the frequency of presence of classical risk factors to their total absence or irrelevance in these populations. Therefore it is imperative to undertake population-based, prospective studies in developing countries such as India to identify CAD risk factors, both conventional and novel[1]. The conventional risk factors namely hypertension, diabetes mellitus (DM), hypertriglyceridaemia, low levels of HDL-C, central obesity, lipoprotein-a (Lp-a), high LDL-C, low levels of antioxidants (vitamin A, E, β - carotene), rising affluence, rapid modernization associated with sedentary but stressful life-style are suggested asrisk factors for CAD. Infections like Chlamydia in association with yet unknown agents may be the other etiological factors. They too do not fill all the gaps in information[2-8]. Heart rate variability (HRV) is one such novel noninvasive method. HRV is the hearts response to the activity of the autonomic nervous system (ANS). The decrease in HRV is a clinical predictive factor of overall cardiac mortality, and especially that ofarrhythmic complications[9]. Recent data also show that analyses of HRV by new methods based on nonlinear dynamics may perform even better than the traditional measures in risk stratification[10]. It helps to assess the balance between sympathetic mediators of heart rate (HR) regulation like epinephrine and norepinephrine, and parasympathetic mediators like acetylcholine. The sympathetic mediators act on sino-atrial and atrio-ventricular nodes, increasing the rate of impulse generation at SA node and reducing the conduction time at AV node thus increasing the HR[11]. Percutaneous transluminal coronary angioplasty (PTCA) is the most commonmodality of treatment of advanced CAD, its effect on HRV has not been investigated. During PTCA mechanical obstruction in the coronary artery is removed followed byinsertion of stent. This exercise is aimed at restoring near normal blood flow. It'slikely that removal of obstruction in major blood vessel supplying a vital organ couldreduce the sympathetic activity tilt the sympathovagal balance towards vagaldominance.

Objectives

To compare the Heart Rate Variability of normal subjects with patients havingcoronary artery disease. Study of changes in Heart Rate Variability after percutaneous transluminal coronary angioplasty.

Review of Literature

Cardiovascular disease (CVD) has emerged as a major health burden worldwide. Within the Indian subcontinent, there has been a rapid rise in prevalence of CAD. TheChennai Urban Population Study (CUPS) carried out in 1262 individuals > 20 years ofage showed the prevalence of CAD to be 11% while the age-adjusted prevalence ratewas 9.0%. Thus the prevalence of CAD appears to be ten times higher in India compared to that reported 40 years ago. The prevalence of CAD in urban Indians is fast approaching the figures reported in migrant Indians[12]. The disease pattern is severe and diffuse in the Indians. CAD is affecting Indians 5-10 years earlier than other communities. They also show higher incidence of hospitalization, morbidity, and mortality than other ethnic groups[13]. The WHO has estimated that India lost 9 billion USD in national income from premature deaths due to heart disease, stroke anddiabetes in the year 2005. These losses are expected to cumulatively lead to 237 billion USD over the next 10 years[14]. These estimates highlight the need for aggressive strategies for the prevention and control of CAD in India. India as a consequence of urbanization may partly explain the escalation of CAD. India is at present experiencing an epidemiological transition with high rates of urbanization. This has led to economic improvement with consequent increased fast food consumption, tobacco usage

and decreased physical activity[15]. The non surgical treatment of arteries narrowed by atherosclerosis was introduced in1964, when Dotter and Judkins performed transluminal angioplasty of femoral arterystenosis in 1970s, Gruntzig modified the dilatation catheter to allow its use in coronary arteries, and in 1977 he performed the first percutaneous transluminal coronary angioplasty (PTCA). The consequences of ischemia and reperfusion involve the subendocardial layer, location of vagal nerve endings. Then they propagate to subepicardial regions. Thus,the assumption that lowered parasympathetic modulation of the sinus node in the earlyperiod following PTCA is a consequence of the rapid changes in blood flow. The impact of ischemia on myocardial performance during angioplasty is seen within a short time period. The findings of the studies published by Kanadasi et al.[16], Osterhues et al.[17] and Wennerblom et al.[18] showing a gradual increase in parasympathetic tone accompaniedby a drop in sympathetic activity in the long-term follow-up suggest a delayed restoration of normal autonomic activity as a consequence of successful coronary revascularisation. The results of these reports indicate an improvement in vagal function although complete functional restoration was not achieved. This may supportthe thesis that myocardial ischemia is not the only mechanism of reduced parasympathetic tone in uncomplicated coronary artery disease.

Material and Methods

The study was conducted in the Department of Cardiology, All india institute of medical sciences, New Delhi. Study duration of Two and half years. Thirty patients with TMT positive/angiographically proven CAD admitted for elective Percutaneous Transluminal Coronary Angioplasty (PTCA) satisfying the inclusion and exclusion criteria in the age group of 40 to 65 years served as cases. The control group consisted of age, anthropometrically matched and TMT negative subjects whosatisfied the inclusion and exclusion criteria.

Inclusion Criteria

Male patients admitted to the hospital with TMT positive for inducible angina and angiography with a single vessel block of more than 70% were screened. Patients satisfying the exclusion criteria in the age group of 40 to 65 years were recruited for the study. The sample size of 30 was determined based on the projected availability ofpatients during the period of study.

Subjects undergoing master health check up in the comparable age without history of coronary artery disease, negative for inducible angina on TMT satisfying exclusion criteria were recruited as controls.

Exclusion Criteria

Previous history of heart failure, cardiac arrhythmias, valvular disease, congenitalheart disease, history of M I, Pacemaker implantation.

Respiratory, endocrine and renal disorder, Patients on drugs modifying autonomic functions.

H/o of consumption of alcohol, Athletes, Obesity.

A detailed history was taken as per the proforma (enclosed). During history taking details of present illness, smoking consumption of alcohol, diet, physical activity/exercise, family history of CAD were noted.

Results

The present study was conducted with 30 cases and 30 control subjects. The age of the

cases was 53.97 ± 6.42 and that for the control subjects was 54.20 ± 6.38 yrs. The height in meters was 1.59 ± 0.48 and 1.58 ± 0.58 in cases and controls respectively. The weight in Kg was 64.93 ± 6.91 and 62.40 ± 6.42 in cases and controls respectively. The Body Mass Index was 25.69 ± 2.57 kg/m^2 and 24.86 ± 2.68 kg/m^2 in cases and controls respectively. There was no statistically significant difference between cases and controls in the Anthropometric parameter. The waist hipratio was 0.88 ± 0.87 m in the cases and 0.88 ± 0.05 m in the controls Comparison of Heart rate variability parameters between cases and controlsThe resting heart rate in beats/min in cases and controls were 88.77 ± 4.20 and 75.23±6.17 respectively. It was significantly higher in the cases p< 0.001. The values of SDNN in the cases were 20.08 ± 7.43ms and in the0 control was 39.51 ± 11.50ms. SDNN was significantly higher in the controls. The values for rMSSD in the cases and controls are 12.62 ± 7.77 and 30.66 ± 12.74 (p<0.001). The value of pNN50 in the cases and controls was found to be 1.92 ± 4.19 and 9.89±6.53 (p < 0.001). In the frequency domain the value of LF in the cases and controls were 67.95±14.12 and 60.73 ± 12.38 respectively (p< 0.04). The value HF in the cases and controls were 31.98±14.12 and 39.03 ± 12.54 (p< 0.004). The ratio of LF/HF in the cases and controls was 2.70 ± 1.26 and 1.82 ± 1.03 respectively (p< 0.004). Comparison of SDNN ms in cases without and with DM was found to be 21.81±7.49 and 14.40 ± 3.43 respectively. Comparison of rMSSD in without and with DM was found to be 13.90 ± 8.37 and 8.41 ± 2.85 respectively. Comparison of pNN50 in without and with DM was found to be 2.50 ± 4.650 and .00±.000 respectively. Comparison of LF n.u in without and with DM was found to be 69.75 ± 13.78 and 62.01 ± 14.63 respectively. Comparison of HF n.u in without and with DM was found to be 30.17 ± 13.79 and 37.92 ± 14.60 respectively. Comparison of LF/HF ratio in without and with DM was found to be 2.91 ± 1.21 and 2.01 ± 1.24 respectively. However these values were not significant. Comparison of HRV parameters in controls without and with DM was found to be 40.69 ± 11.14 and 34.77 ± 12.77 respectively. Comparison of rMSSD in without and with DM was found to be 32.47 ± 12.46 and 23.42 ± 12.21 respectively. Comparison of pNN50 in without and with DM was found to be 9.91 ± 5.71 and 9.82 ± 9.86 respectively. Comparison of LF n.u in without and with DM was found to be 60.40±12.96 and 62.03 ± 10.66 respectively. Comparison of HF n.u in without and with DM was found to be 40.28 ± 13.05 and 34.04 ± 9.585respectively. Comparison of LF/HF ratio in without and with DM was found to be 1.82±1.09 and 1.79±8.88 respectively. However these values were not significant. Correlation between Heart Rate Variability parameters and lipid profile in cases In time domain SDNN had negative correlation with CHO r = -0.18, TGL r = -0.31, LDL r = -0.18, VLDL r = -0.10, HDL r = -0.03, CHO/HDL ratio r = -0.21. rMSSD had positive correlation with CHO r = 0.072, LDL r = 0.014, VLDL r = 0.134, HDL r = 0.071, CHO/HDL ratio r = 0.020 and a negative correlation with TGL r = - 0.13. pNN50 had positive correlation with CHO r = 0.039, VLDL r = 0.138, HDL r = 0.093, CHO/HDL ratio r = 0.009. In the frequency domain LF had positive correlation with CHO r = 0.008, LDL r = 0.059, HDL r = 0.149, a negative correlation with TGL r = -0.12, VLDL r = -0.113, CHO/HDL ratio r = -0.072. In HF a positive correlation with TGL r = 0.117, VLDL r = 0.109, CHO/HDL r = 0.070 and a negative correlation with CHO r = -0.012 LDL r = -0.063, HDL r = -0.149. LF/HF ratio had positive correlation with CHO r = 0.069, TGL r = 0.063, LDL r = 0.065, VLDL r = 0.018, HDL r = 0.231 and a negativecorrelation with CHO/HDL ratio r = -0.259. However no significance was found between HRV and these parameters.

Anthropometric parameters in Controls and Cases

Anthropometric parameters	Controls	Cases	P value
Age in years	54.20±6.38	53.97±6.42	t=0.02,p=0.88

Height in m	1.58±0.05	1.59±0.04	t=0.11,p=0.73
Weight in kg	*62.40±6.42*	64.93±6.91	t=2.16,p=0.14
BMI (kg/m^2)	24.86±2.68	25.69±2.57	t=1.48,p=0.22
Waist/Hip ratio	0.88±0.05	0.88±0.87	t=0.034,p=0.85

Comparison of HRV parameters between the cases and controls

HRV parameters	**Cases n=30**	**Controls n=30**	**P value**
HR beats/min	88.77±4.20	75.23±6.17	t=98.43,p<0.001
SDNN ms	20.08±7.43	39.51±11.50	t=60.33,p<0.001
rMSSD	12.62±7.77	30.66±12.74	t=43.79,p<0.001
pNN50	1.92±4.19	9.89±6.53	t=31.64,p<0.001
LF ms^2	51.50±44.95	45.87±35.50	t=0.290,p<0.592
HF ms^2	21.47±19.00	33.20±33.34	t=2.803,p<0.04
LF n.u	67.95±14.12	60.73±12.38	t=4.42,p<0.04
HF n.u	31.98±14.12	39.03±12.54	t=4.17,p<0.046
LF/HF ratio	2.70±1.26	1.82±1.03	t=8.79,p<0.004

Comparison of HRV parameters in cases with and without DM

		N	Mean±SD	't' value	'p' value
SDNN ms	No DM	23	21.81±7.49	6.321	0.018
	Yes DM	7	14.40±3.43		
rMSSD	No DM	23	13.90±8.379	2.838	0.103
	Yes DM	7	8.41±2.85		
pNN50	No DM	23	2.50±4.65	1.981	0.170
	Yes DM	7	.00±.00		
LF n.u	No DM	23	69.75±13.78	1.649	0.210
	Yes DM	7	62.01±14.63		
HF n.u	No DM	23	30.17±13.79	1.651	0.209
	Yes DM	7	37.92±14.60		
LF/HF Ratio	No DM	23	2.91±1.21	2.887	0.100
	Yes DM	7	2.01±1.24		

Comparison of HRV parameters in cases with and without DM

		N	Mean± SD	't' value	'p' value
SDNN	No DM	24	40.69±11.14	1.282	0.267
	Yes DM	6	34.77±12.77		
rMSSD	No DM	24	32.47±12.46	2.548	0.122
	Yes DM	6	23.42±12.21		
pNN50	No DM	24	9.91±5.71	.001	0.975
	Yes DM	6	9.82±9.86		
LF n.u	No DM	24	60.40±12.96	.080	0.779
	Yes DM	6	62.03±10.66		
HF n.u	No DM	24	40.28±13.05	1.193	0.284
	Yes DM	6	34.04±9.58		
LF/HF Ratio	No DM	24	1.82±1.09	.004	0.950

Discussion

CAD is a major cause for morbidity and mortality in both the developing and the

developed countries. Death due to CAD is assuming epidemic proportions in view of a significant change in lifestyle and food habits. Sedentary lifestyles associated with stress, consumption of saturated fat are blamed to be the major risk factors for CAD.Habits like smoking, indiscriminate consumption of alcohol also contribute to degenerative changes in the blood vessel resulting atherogenesis leading to CAD[3]. Itis reported that major part of the government exchequer has to be spent on managingsubjects with CAD and serious complications arising out of the disease[18]. The list of risk factors is long and never ending. However, closer looks at these factors indicate that a major part of the risk factors are modifiable. A clear understanding of the impact of these risk factors will go a long way in preventing theoccurrence of the disease and reduce the burden on government spending. In additionto the classical risk factors a few novel risk factors have been proposed to assess the seriousness of the CAD and also used as a tool to predict the outcome of the disease. One such novel risk factor is to assess the HRV. The study of HRV is done broadly under two categories, time domain parameters and frequency domain parameters. Time domain parameters indicate the HRV over a period of 24 hours. It is useful in detecting alteration in the circadian rhythm. The frequency domain parameters help toassess the activity of sympathetic nervous system, parasympathetic nervous system and sympathovagal balance over shorter time intervals[11]. It has been reported that CAD is associated with reduced parasympathetic activity andsympathetic predominance. The earlier reports have indicated reduction ofparasympathetic activity with or without sympathetic over activity [18,]. The CAD with reduced HRV can also point towards a poor prognosis without a timely intervention. HRV parameters were analysed in age and anthropometrically matched control subjects. The time domain parameters and the frequency domain parameters were analysed. rMSSD and pNN50 was higher in controls. In the frequency domain parameters LF and LF/HF ratio were lower and HF ratio was higher inn controls. These observations in time and frequency domain parameters indicate a higher parasympathetic activity and parasympathetic predominance in controls as comparedto cases. PTCA is one of the time tested procedures to remove the block in coronary artery andestablish a reperfusion[19]. The effect of PTCA on HRV has not been studied on the Indian population. The observation by the earlier studies on the effect of removal of the block has been confusing and conflicting. Ali Aydinlar et al have reported the shift of HRV from sympathetic predominance to increased parasympathetic activity immediately following the deflation of the balloon. Osterhues et al have observed nochange in HRV after PTCA[17]. Kanadasi et al have reported the first observable change in HRV occur 10 days following PTCA[16]. Sedziwy et al have observed a change in HRV with increased parasympathetic activity sustained even after a year following PTCA. Vagal activation exerts an antifibrillatory effect; sympathetic activation does the opposite. Comparing the values between left coronary artery and left circumflex artery, the LCA was found to have higher rMSSD, pNN50, HF and lower LF and LF/HF ratio indicating a higher parasympathetic tone in LCA. However, the exact mechanism leading to these changes is not known. Some of the previous studies also have reported no correlation between the artery involved and HRV. The earlier studies have reported that diabetes is a confounding variable that influences HRV. It is commonly accepted that diabetic patients and those with diabetes-induced autonomic neuropathy present impaired capacity for vasodilatationand reduced coronary flow. However, a study by Szot et al., resembling our study, didnot reveal a significant impact of diabetes mellitus on the values of HRV parametersin response to PTCA[20]. It can also throw light on the extent of influence of other confounding variables on the development of CAD and complications arising out of the disease.

Conclusion

In our study, control subjects had a higher parasympathetic activity, reduced sympathetic activity with sympathovagal balance exhibiting parasympatheticdominance. Patients with CAD had greater sympathetic activity reduced parasympathetic activity tilting the sympathovagal balance towards sympathetic dominance. On first day following PTCA, there was no significant alteration in the autonomic function. On 3rd day following PTCA, there was an increase parasympathetic activity and reduced sympathetic activity tilting the balance towardsparasympathetic dominance.

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