Original article

# Heart Rate Variability in Patients with Coronary Artery Disease and Effect of Percutaneous Coronary Angioplasty

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## ABSTRACT

Background: In coronary artery disease (CAD), the balance between the sympathetic and parasympathetic nervous systems is disturbed with sympathetic predominanace. Sympathetic over-activity is eliminated through percutaneous coronary angioplasty (PCA). Heart rate variability is a novel method for evaluating cardiac autonomic dysfunction. The study investigated the impact of percutaneous coronary angioplasty (PCA) on cardiac autonomic dysfunction by comparing heart rate variability patterns in stable and unstable angina patients before and after the procedure.

Subjects and methods: An experimental study involving 34 males with stable angina (Group 2), 34 males with unstable angina (Group 3), and 34 healthy males (Group 1) was carried out at Punjab Institute of Cardiology, Lahore, between July 2018 and August 2019. While patients with angina underwent PCA, the healthy group did not. The Holter DMS 300-3A was utilised to record the ECG for five minutes. For Groups 2 and 3, ECG was recorded before PCA, as well as 24 hours and two weeks following angioplasty. Cardioscan Premier12 by DM Software was used to analyse the Holter ECG recordings in both the time (SDNN, RMSSD, $NN_{50}$, $PNN_{50}$, and SDNN: RMSSD) and frequency domain indices (HF, LF, and LF: HF). The data was statistically analyzed using the computer programme IBM SPSS statistics version 20.

Results: HRV metrics SDNN, RMSSD, $NN_{50}$, $pNN_{50}$, LF, HF each (p-value <0.001) were increased and LF: HF (p-value <0.001) was lower in Group 1 than in angina groups. Group 2 and Group 3 showed statistically significant improvements (p-value<0.05) in HRV metrics SDNN, HF, and LF: HF 24 hours after PCA. At 2 weeks post PCA, statistically significant results (p-value <0.05) were found for SDNN, RMSSD, LF, HF and LF: HF in Group 2. Statistically significant results (p-value <0.05) were also found for SDNN, RMSSD, LF, HF, SDNN: RMSSD and LF: HF in Group 3 at 2 weeks after PCA.

Conclusion: Patients with stable and unstable angina have reduced heart rate (HRV) compared to normal individuals. However, after PCA, HRV parameters increase, indicating that illness diminishes HRV, but revascularization through PCA improves it.

Keywords:

Coronary artery disease, Stable and unstable angina, Cardiac autonomic dysfunction, Heart rate variability, Percutaneous coronary angioplasty

## INTRODUCTION

Coronary Artery Disease (CAD) is the leading cause of mortality, primarily occurring in low and middle-income countries.[1] Stable angina is described as chest pain or discomfort produced by exertion and alleviated by rest or nitroglycerin. While unstable angina is severe, frequent, or persistent pain, waking the patient.[2] The condition involves the gradual constriction of coronary arteries due to the formation of atherosclerotic plaques, resulting in impaired blood supply to the heart muscle and ischemic episodes.[3]

There is a delicate balance between the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) to regulate heart rate and its variability.[4] The autonomic nervous system's activity of the heart is measured by the non-invasive, and trustworthy method called HRV.[5] Reduced HRV strongly predicts death and major adverse cardiac events and is caused by an imbalance between the SNS and the PNS.[6] The time domain approach is the simplest way of measurement of HRV and it takes the average of the highest and lowest intervals from a continuous ECG recording over a defined time.[7] QRS complexes from the ECG are used

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in the frequency domain. These complexes are subjected to the Fourier Transformation, which turns ECG data into waveforms of varying frequencies.[5] It displays how much signal energy falls inside a given frequency band over a range of frequencies.[8] Percutaneous coronary intervention is done in individuals with stable angina if medical therapy fails or symptoms worsen[9], whereas it is suggested in patients with unstable angina if they have recurrent angina at rest or during low-level activity despite rigorous medical treatment.[10] Successful PCI improves the autonomic function of the heart and reduces mortality in people with coronary artery anomalies.[11] This research contributes that ischemia-induced autonomic alterations cause reduction in HRV and reversal of ischemia-induced autonomic alterations by angioplasty improves autonomic balance.

## SUBJECTS AND METHODS

An experimental study was conducted at the Punjab Institute of Cardiology, Lahore from July 2018 to August 2019. The patients were enrolled from the angiography ward and admitted for angioplasty using a non-probability convenient sampling technique. The sample size of 102 subjects was calculated using the time domain variable (SDNN) of heart rate variability[12] at 90% power of study, 95% confidence interval and 5% level of significance. An informed written consent was taken from each participant. History and general physical examination were conducted and results were recorded on proforma. Age-matched males were included due to gender differences in autonomic modulations. The study included 34 healthy males due to insufficient HRV data in local normal individuals, based on history, physical examination, and ECG. Group 2 and Group 3 included 34 male subjects with stable angina and unstable angina respectively, selected for elective PCI based on history, clinical examination, and coronary angiograms within a year, with a left ventricular ejection fraction of 50%-70%. The patients with prior PCI or coronary artery bypass surgery (CABG) and those with a history of comorbidities like cardiomyopathies, arrhythmias, myocardial infarction, depression, diabetes mellitus, renal failure, respiratory failure and hepatic failure were excluded. Patients undergoing HRV recordings were advised to avoid coffee, tea, chocolates, alcohol, smoking, and vigorous exercise for at least 12 hours before Holter recording.[13] HRV was monitored at 8:00 to 11:00 am in a supine position with normal quiet breathing and a peaceful mind in a quiet room.[14] Measurements of HRV were performed thrice, firstly before PCA, secondly at 24 hours after PCA and thirdly at 2 weeks post-PCA.[15] Standard Lead A system involves the placement of 7 electrodes on the chest with subjects given 5 minutes of rest before recording ECG.[14] DMS 300-3A Holter recorder was used to record ECG. The ECG data was transferred to a computer via a PCMCIA card, scanned and manually edited to ensure only normal-to-normal beats were included in the analysis.[16] Recordings of ECG were analyzed using DM Software Cardioscan Premier12 in both time domain and frequency domain indices.

Time domain parameters of HRV were SDNN (standard deviation of normal-to-normal RR intervals and sensitive to changes in cardiac sympathetic and parasympathetic nerve activity). RMSSD (root-mean-square differences of successive R-R intervals and reflects parasympathetic activity). $NN_{50}$ (number of interval differences of successive NN intervals greater than 50ms and reflects parasympathetic activity). $PNN_{50}$ (percentage of R-R intervals differing >50ms from the preceding one and reflects parasympathetic activity). SDNN: RMSSD reflects the sympathovagal balance. It is equivalent to LF: HF. The frequency domain parameters of HRV were HF (high frequency (0.15-0.40Hz) related to the respiratory sinus arrhythmia and is thought to reflect parasympathetic activity. Vagal mediators exert their influence more quickly on the heart). LF (low frequency (0.04-0.15Hz). LF is sensitive to changes in cardiac sympathetic and parasympathetic nerve activity. Sympathetic mediators exert their influence over a longer time). LF: HF ratio (an index of the relationship between sympathetic and parasympathetic neuronal activity. It is equivalent to SDNN: RMSSD)

The data was analysed using the computer programme IBM SPSS statistics version 20, and $p< 0.05$ was taken as statistically significant. Normally distributed data was presented as mean ± standard deviation and was determined by the Kolmogorov-Smirnov Test. One-way ANOVA test and Kruskall Wallis test were used to evaluate variables with normal distribution and with non-normal distribution respectively. Differences in means of pre-PCA and post-PCA values were compared using paired t-tests. Non-normally distributed variables, pre-PCA and post-PCA were compared using the Wilcoxon sign rank test.

## RESULTS

The age of subjects in the current study was not significantly different in the three groups with p-value =

0.739. The mean age of normal individuals in Group 1 was 41.52 ± 5.98, in Group 2 (stable angina) was 41.05 ± 5.69 and in Group 3 (unstable angina) was 40.47 ± 5.14. Each group consists of 34 distinct participants.

The initial readings of HRV parameters (pre-PCA) for the three groups are mentioned in Table 1. One-way ANOVA expressed in mean ± SD showed a statistically significant difference (p-value ≤0.05) for SDNN, RMSSD and HF. Kruskall Wallis test showed statistically significant results for $NN_{50}$, $pNN_{50}$, LF and LF: HF expressed in madian (IQR).

Tukey's test and Dunn's test were applied for pair-wise comparison followed by ANOVA for SDNN, RMSSD and HF with statistically significant difference (p≤0.05) between (group 1 and group 2) and (group 1 and group 3) and for $NN_{50}$, $pNN_{50}$, LF and LF: HF with significant difference (p-value ≤0.05) for $NN_{50}$, $pNN_{50}$, LF and LF: HF between (group 1 and group 2) and (group 1 and group 3) respectively. According to these findings, healthy people had higher levels of SDNN and LF (representing total autonomic activity), RMSSD, HF, $NN_{50}$, and $pNN_{5}0$ (reflecting parasympathetic activity), and lower levels of LF: HF (reflecting sympathovagal activity).

Paired t-test for normally distributed data expressed in mean ± SD and Wilcoxon signed rank test for non-parametric data taken in median and IQR were performed on Group 2 and Group 3 for comparing the values obtained before PCA and 24 hours after PCA. Table 2 showed statistically significant results p≤0.05 for SDNN, HF and LF: HF in Group 2 reflecting improved sympathovagal balance. Group 3 showed statistically significant results p≤0.05 for SDNN. HF and LF: HF manifesting reversal of ischemia causes improvement in parasympathetic activity and overall autonomic balance 24 hours after PCA.

A paired t-test for data of normal distribution and Wilcoxon signed rank test for data of non-normal distribution were performed on Group 2 and Group 3 for comparing the values obtained before PCA and 2 weeks after PCA. Statistically significant results p≤0.05 were found for SDNN, RMSSD, SDNN: RMSSD, LF, HF and LF: HF in Group 2 and for SDNN: RMSSD and LF: HF in Group 3. After two weeks, an increasing number of variables exhibit significant outcomes, indicating further improvement in autonomic balance.

Table 1: Comparison of HRV parameters among group 1, group 2 and group 3

| Parameters | Group 1 | Group 2 | Group 3 | p-value |
|---|---|---|---|---|
| **Time domain** | | | | |
| SDNN (ms) | 69.9 ± 13.6 | 48.44 ± 12.6 | 43.6 ± 17.4 | 0.001[a*] |
| RMSSD (ms) | 50.9 ± 14.8 | 33.94 ± 12.6 | 34.4 ± 17.9 | 0.001 [a*] |
| SDNN/RMSD | 1.47 (1.2-1.6) | 1.6 (1.1-1.9) | 1.24 (1.1-1.9) | 0.470[b] |
| $NN_{50}$ (count) | 85.5 (52.8-108.8) | 19.5 (5.8-43.8) | 18 (3.0-52.5) | 0.001[b*] |
| $pNN_{50}$% | 26.0 (13.5-36.3) | 6.0 (1.8-15.5) | 5 (0.0-18.25) | 0.001 [b*] |
| **Frequency domain** | | | | |
| LF ($ms^2$) | 976.4 (699.5-1360.4) | 419.80 (307.6-612.1) | 407.1 (350.3-451.5) | 0.001[b*] |
| HF ($ms^2$) | 588.7 ± 231.26 | 130.7 ± 50.3 | 81.39 ± 21.7 | 0.001[a*] |
| LF/HF | 1.82 (1.52-2.1) | 3.18 (2.6-5.0) | 5.76 (3.7-6.5) | 0.001 [b*] |

a = comparison done by One-way ANOVA
b = comparison done by Kruskall Wallis
* = statistically significant
n=34 (each group)
Group 1=healthy subjects, Group 2=stable angina and Group 3=unstable angina

Table 2: Comparison of HRV parameters before and 24 hours after PCA in Group 2 as well as in Group 3

| HRV Parameters | Group 2 (pre-PCA) | Group 2 (24 hours after PCA) | p-value | Group 3 (pre-PCA) | Group 3 (24 hours after PCA) | p-value |
|---|---|---|---|---|---|---|
| **Time domain** | | | | | | |
| SDNN (ms) | 48.44 ± 12.61 | 52.82 ± 12.62 | 0.044[a*] | 37.94 ±15.81 | 43.64 ±17.42 | 0.043[a*] |
| RMSSD (ms) | 33.94 ± 12.07 | 37.79 ± 10.90 | 0.172[a] | 34.35 ±17.96 | 31.59 ±15.21 | 0.230[a] |
| SDNN/RMSSD | 1.54 ± 0.52 | 1.47 ± 0.43 | 0.528[a] | 1.24 (1.06-1.88) | 1.23 (0.92-1.62) | 0.238[b] |
| $NN_{50}$ (count) | 19.5 (5.75-43.75) | 23 (5.75-42.50) | 0.891[b] | 18 (3.00-52.50) | 12 (4.00-31.75) | 0.095[b] |
| $pNN_{50}$% | 6 (1.75-15.50) | 6.5 (1.75-18.75) | 0.296[b] | 5 (0.00-18.25) | 4.5 (1.00-11.00) | 0.061[b] |
| **Frequency domain** | | | | | | |
| LF ($ms^2$) | 419.8 (307.62-612.05) | 305.5 (180.10-593.45) | 0.174[b] | 407.1 (350.32-451.50) | 320.15 (154.85-575.57) | 0.447[b] |
| HF ($ms^2$) | 130.70 ± 50.34 | 186.26 ± 113.54 | 0.009[a*] | 77.8 (68.55-94.92) | 142.8 (62.57-278.07) | 0.001[b*] |
| LF/HF | 3.18 (2.55-5.00) | 2.46 (1.35-3.50) | 0.001[b*] | 5.76 (3.71-6.49) | 1.93 (1.58-3.05) | 0.001[b*] |

a = comparison done by Paired t-test
b = comparison done by Wilcoxon signed-rank test
* = statistically significant
Group 2=stable angina and Group 3=unstable angina
=34 (each group)

Table 3: Comparison of HRV parameters before and 2 weeks after PCA in Group 2 as well as in Group 3

| HRV parameters | Group 2 (pre-PCA) | Group 2 (2 weeks after PCA) | p-value | Group 3 (pre-PCA) | Group 3 (2 weeks after PCA) | p-value |
|---|---|---|---|---|---|---|
| **Time Domain** | | | | | | |
| SDNN (ms) | 48.44 ± 12.61 | 55.35 ± 12.54 | 0.001[a*] | 43.64 ± 17.42 | 49.94 ±16.01 | 0.007[a*] |
| RMSSD (ms) | 33.94 ± 12.07 | 45.29 ± 13.69 | 0.001[a*] | 34.35 ± 17.96 | 47.97±19.15 | 0.001[a*] |
| SDNN/RMSSD | 1.6 (1.11-1.91) | 1.19 (1.03-1.66) | 0.054[b] | 1.24 (1.06-1.88) | 1.1 (0.76-1.45) | 0.005[b*] |
| $NN_{50}$ (count) | 19.5 (5.75-43.75) | 23 (7.75-65.00) | 0.274[b] | 18 (3.00-52.50) | 14.5 (4.00-81.00) | 0.152[b] |
| $pNN_{50}$ % | 6 (1.75-15.50) | 7.5 (2.00-28.25) | 0.128[b] | 5 (0.00-18.25) | 5.5 (0.75-28.25) | 0.234[b] |
| **Frequency Domain** | | | | | | |
| LF ($ms^2$) | 419.8 (307.62-612.05) | 342.45 (251.10-435.20) | 0.001[b*] | 406.81 ± 81.91 | 349.79±66.24 | 0.001[a*] |
| HF ($ms^2$) | 130.70 ± 50.34 | 188.30 ± 68.49 | 0.001[a*] | 81.39 ± 21.76 | 132.46±38.26 | 0.001[a*] |
| LF/HF | 3.18 (2.55-5.00) | 1.77 (1.60-2.09) | 0.001[b*] | 5.76 (3.71-6.49) | 2.65 (2.16-3.26) | 0.001[b*] |

a = comparison done by Paired t-test
b = comparison is done by Wilcoxon signed-rank test
* = statistically significant
Group 2=stable angina
Group 3=unstable angina
n=34 (each group)

## DISCUSSION

This study aimed to assess the effect of PCA on HRV in individuals with stable and unstable angina. The study revealed significantly decreased values of SDNN, RMSSD, $NN_{50}$, $pNN_{50}$, LF, and HF in both the diseased groups whereas, LF: HF and SDNN: RMSSD were increased when compared with the healthy group. Individuals in Group 1 (healthy individuals) in the current study were in a good state of sympathovagal balance reflected by the values of parameters of HRV being comparable with other studies. One study quoted reference values of HRV parameters like SDNN, RMSSD, LF, HF, and LF:HF. The values mentioned by the author were comparable with our study. Another study compared ultra-short-term HRV (1 min. recording) with short-term HRV (5 min recording) in terms of SDNN and RMSSD. The values of SDNN and RMSSD in 5 min recordings were also comparable with our studies.[17,18]

Findings of this study shown reduced HRV in Group 2 (stable angina) and Group 3 (unstable angina) manifesting autonomic imbalance. Markers of the parasympathetic stem (HF, RMSSD, $NN_{50}$, and $pNN_{50}$) were significantly ($p<0.001$) reduced in both angina groups in comparison to the normal group. Likewise, SDNN and LF were also significantly reduced ($p<0.001$) in Group 2 (stable angina) and Group 3 (unstable angina) as compared to Group 1 (healthy individuals). It was seen from the literature that sympathoexcitation as well as reduction in parasympathetic activity occurs as a result of ischemia/injury.[19] Augmented norepinephrine release occurred as a result of sensory signal transduction from ischemic myocardial tissue, resulting in reflex-mediated augmentation of sympathoexcitation, which could be accountable for the higher incidence of arrhythmias.[20] A study on CAD patients undergoing elective coronary angiography discovered a negative connection among coronary artery stenosis, $pNN_{50}$ and HF.[21] This finding implied that the degree of coronary atherosclerosis was linked to a shift in cardiac autonomic regulation toward vagal withdrawal and sympathetic predominance, even in people with no symptoms of myocardial ischemia. This study supports our findings in terms of vagal withdrawal. Current study also outlined that the state of autonomic imbalance was reversed by recanalization indicated by improvement in initially reduced HRV. Afferents from cardiac mechanoreceptors produced an increase in sympathetic discharge at the heart due to metabolic product buildup. Restoration of blood flow to the myocardium by PCA reduced previously enhanced sympathetic activity and augmented vagal outflow. [22]

In the Group 2 at 24 hours after PCA, the parasympathetic increment was indicated by a statistically significant rise in HF ($p=0.009$). Although RMSSD and $pNN_{50}$ were also increased but failed to achieve statistical significance ($p=0.172$ and $p=0.296$). Significant increases in SDNN ($p=0.04$) and decreases in LF: HF ($p<0.001$) were also seen in this group, however their contribution to sympathetic and parasympathetic components was unclear. At 24hr. after PCA, LF was also increased but unable to achieve statistical significance ($p=0.174$). The Group 3 also showed a significantly raised value of HF ($p<0.001$) reflecting an increased parasympathetic component whereas a significantly decreased value of LF: HF ($p=0.001$) and increased value of SDNN ($p=0.043$) manifesting shift of sympathovagal balance towards normal at 24 hours post-PCA. Improved sympathovagal balance was indicative of better cardiac autonomic

function and hence reduced morbidity and mortality. A pre and post-intervention study has been carried out in India on patients with age 40-65 years, suffering from single vessel stenosis of more than 70%.[23] They did not notice any significant difference between pre-PCA and post-PCA HRV variables recorded after 24 hours. They ascribed this discovery to partial blood flow restoration through PCA, patient selection, and the existence of collaterals around stenosed arteries. They further concluded that improvement in autonomic neuronal activity was observed as soon as on 3rd day after PCA. A significant rise in SDNN, RMSSD, and HF, decrement in LF, and no significant change in $pNN_{50}$ were ascertained on 3rd post-PCA day. Results of current study showed improvement in HRV values as early as 24 hrs. after PCA. This may be due to complete blood flow restoration through PCA and presence of less severe disease in our study population.

Another pre-post study suggested that patients with chronic stable angina had autonomic dysfunction before revascularization.[24] However, PCA enhanced cardiac autonomic functions were dramatically represented by increased values of SDNN, RMSSD, $pNN_{50}$ and HF and significantly decreased value of LF. In these patients, results suggested improvements in autonomic reactivity. These findings are in accordance with those observed in this study. More calcified lesions might require aggressive handling during PCA, increasing ischemic burden and delaying early recovery of HRV parameters. Moreover, prolonged tight stenosis and ischemia further worsened the situation. Reperfusion in these cases posed further damage because of already present oxidative reactive species and WBCs in the blood[25]. In our study SDNN, RMSSD, HF were raised and SDNN:RMSSD, LF, LF:HF were reduced significantly ($p<0.05$). The reason might be the presence of less severe disease and successful PCA without any complication in our study participants.

## CONCLUSION

The patients of stable and unstable angina have reduced HRV as compared to normal individuals. There is a considerable increase in HRV parameters reflecting improved sympathovagal balance 24 hours after PCA, with continued improvement after 2 weeks in Group 2 and Group 3. It suggests that the illness process diminishes HRV, but recovery from ischemia via revascularization through angioplasty improves HRV.

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