

# A Study of Cardiac Autonomic Functions in Patients with Chronic Stable Angina Undergoing Percutaneous Coronary Revascularization

## Perkütan Koroner Revaskülarizasyon Geçiren Kronik Stabil Anjinal Hastalarda Kardiyak Otonomik Fonksiyonlar Üzerine Bir Çalışma

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### ABSTRACT

**Objective:** In the present study, cardiac autonomic functions in CSA patients were evaluated before and after percutaneous coronary intervention (PCI) using heart rate variability (HRV).

**Methods:** Thirty patients with CSA were recruited from cardiology outpatient clinics of VMMC and Safdarjung hospital, New Delhi, India. For each patient HRV parameters (LF, HF, LF:HF ratio, SDNN, RMSSD, total power, and pNN50) were gathered before and after PCI. Data were compiled and analyzed using licensed statistical software: SPSS version 21.0.

**Results:** Out of 30 subjects, SDNN ( $61.47 \pm 22.27$  vs.  $32.24 \pm 16.50$ ms,  $p < 0.0001$ ), RMSSD ( $53.86 \pm 31.41$  vs.  $28.81 \pm 23.80$ ms,  $p = 0.001$ ) and pNN50 ( $46.24 \pm 34.36$  vs.  $5.20 \pm 6.63$ ,  $p < 0.0001$ ) in post-PCI were significantly higher as compared to the pre-PCI values. There were significant increases in both LF ( $1193 \text{ms}^2 \pm 302.04 \text{ms}^2$  vs.  $1054.60 \text{ms}^2 \pm 208 \text{ms}^2$ ,  $p < 0.001$ ) and HF ( $991.57 \pm 872.40 \text{ms}^2$  vs.  $466.72 \text{ms}^2 \pm 257.93 \text{ms}^2$ ,  $p < 0.0001$ ), also in total power ( $3548.37 \text{ms}^2 \pm 807.73 \text{ms}^2$  vs.  $2428 \text{ms}^2 \pm 867.07 \text{ms}^2$ ,  $p < 0.0001$ ) in post-PCI as compared to pre-PCI. The LF:HF ratio in pre-PCI was higher as compared to post-PCI ( $1.467 \pm 1.639$  vs.  $1.143 \pm 0.852$ ,  $p = 0.805$ ), but the difference was not statistically significant.

**Conclusion:** In this preliminary study, it is concluded that there is significant improvement in resting cardiovascular parameters, resting autonomic tone as measured by HRV which shows increase in both parasympathetic as well as sympathetic reactivity following revascularization by PCI in CSA patients. Hence, we also suggest that the use of noninvasive tests such as HRV should be done to stratify further risk of disease progression.

**Keywords:** Sudden cardiac death, heart rate variability, percutaneous coronary intervention, chronic stable angina, autonomic dysfunction

### ÖZ

**Amaç:** Bu çalışmada kronik stabil anjina (KSA) hastalarında kardiyak otonom fonksiyonlar, perkütan koroner girişim (PKG) öncesi ve sonrası kalp hızı değişkenliği (KHD) kullanılarak değerlendirilmiştir.

**Yöntem:** Otuz KSA hastası, Hindistan'da Yeni Delhi'deki VMMC ve Safdarjung hastanesinin kardiyoloji bölümü ayaktan hasta kliniğinden alınmıştır. Her hasta için PKG'den önce ve sonra KHD parametreleri (LF, HF, LF:HF oranı, SDNN, RMSSD, Toplam güç ve pNN50) alınmıştır. Veriler, lisanslı istatistiksel yazılım SPSS sürüm 21.0 kullanılarak derlenerek analiz edilmiştir.

**Bulgular:** Otuz hastadan SDNN ( $61.47 \pm 22.27$  vs.  $32.24 \pm 16.50$ ms,  $p < 0.0001$ ), RMSSD ( $53.86 \pm 31.41$  vs.  $28.81 \pm 23.80$ ms,  $p = 0.001$ ) ve pNN50 ( $46.24 \pm 34.36$  vs.  $5.20 \pm 6.63$ ,  $p < 0.0001$ ) PKG sonrası, PKG öncesine kıyasla anlamlı ölçüde daha yüksek çıkmıştır. Hem LF ( $1193 \text{ms}^2 \pm 302.04 \text{ms}^2$  vs.  $1054.60 \text{ms}^2 \pm 208 \text{ms}^2$ ,  $p < 0.001$ ), hem HF ( $991.57 \pm 872.40 \text{ms}^2$  vs.  $466.72 \text{ms}^2 \pm 257.93 \text{ms}^2$ ,  $p < 0.0001$ ) hem de toplam güçte ( $3548.37 \text{ms}^2 \pm 807.73 \text{ms}^2$  vs.  $2428 \text{ms}^2 \pm 867.07 \text{ms}^2$ ,  $p < 0.0001$ ) PKG öncesi PKG sonrası ile karşılaştırıldığında anlamlı artış çıkmıştır. PKG öncesi LF:HF oranı, PKG sonrasında göre daha yüksek bulunmuştur ( $1.467 \pm 1.639$  vs.  $1.143 \pm 0.852$ ,  $p = 0.805$ ), ancak istatistiksel olarak anlamlı bir fark bulunmamıştır.

**Sonuç:** Bu ön çalışmada, istirahat halinde kardiyovasküler parametrelerde anlamlı iyileşme olduğu, KHD ile ölçülen istirahatteki otonom tonusun, KSA hastalarında PKG ile revaskülarizasyonu takiben hem parasempatik hem de sempatik reaktivitede artış gösterdiği sonucuna ulaşılmıştır. Bu nedenle, KHD gibi girişimsel olmayan testlerin, hastalığın ilerleme riskinin daha katmanlı şekilde değerlendirilmesi için yapılmasını önermekteyiz.

**Anahtar kelimeler:** Ani kardiyak ölüm, kalp hızı değişkenliği, perkütan koroner girişim, kronik stabil anjinal, otonom disfonksiyon

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## INTRODUCTION

Coronary artery disease is a key health concern today and has assumed epidemic proportions worldwide. Recent studies have showed that the prevalence of chronic coronary syndrome (CCS) has been increasing in the Indian population as well. In India, the prevalence of CCS has risen from 1.1% to 7.5% in the urban population and from 2.1% to 3.7% in the rural areas in the last three decades<sup>1</sup>. Chronic coronary syndrome is the main form of coronary artery disease and is of a stable type<sup>2</sup>. In the presence of chronic stable angina (CSA), the probabilities of adverse cardiovascular events such as myocardial infarction and cardiac death increase markedly<sup>3</sup>. CSA presents routinely as uneasiness, discomfort, or a squeezing pain in the chest, which is triggered or aggravated by exertion and is reduced by rest or by drugs such as nitroglycerin<sup>4</sup>. Anginal pain typical of CSA develops as a result of myocardial ischemia, which results in an imbalance between the demand and supply of oxygen to the myocardium. CSA causes severe atherosclerotic narrowing of one or more coronary vessels which is the underlying cause of the ischemic changes<sup>5</sup>. In these patients, imbalance in the autonomic regulation may occur because of chronic ischemia and hypoxia<sup>6,7</sup>. Some studies in the past observed a decrease in heart rate variability (HRV) indices in these patients, whereas others have reported that patients with CSA often have augmented sympathetic influence<sup>8,9</sup>. The chronic state of ischemic myocardium appears to be the reason for this autonomic dysfunction. In myocardial ischemia, the cause of autonomic dysfunction is postulated to be oxygen-deprived myocardium. Therefore, alleviation of this permanent state of autonomic dysregulation is the foremost goal of current treatment strategies for patients with CSA. Literature suggests that myocardial ischemia leads to autonomic dysregulation and that restoring vascularization improves the autonomic functions. Thus, enhancing the myocardial perfusion by percutaneous coronary

intervention (PCI) might have beneficial effects on the recovery of autonomic balance in ischemia-triggered autonomic dysregulation.

To the best of our knowledge, few studies have investigated the autonomic function modulation of the cardiovascular system in patients with CSA and the effect of revascularization by PCI therapy on autonomic functions. The present study aimed to see whether there was an improvement in autonomic functions in patients with CSA who had undergone PCI.

## MATERIAL and METHOD

This is a pre-post study. This research was performed after obtaining ethical clearance from the Institutional Ethical Committee of VMMC and Safdarjung Hospital. The study was conducted from November 2017 to April 2019 in the Department of Physiology in collaboration with the Department of Cardiology, VMMC and Safdarjung Hospital, New Delhi. This investigation included 30 subjects of either sex who had CSA and were in the age group of 45-70 years. They were selected from the patients who visited the cardiology outpatient department of VMMC and Safdarjung Hospital. These subjects were scheduled for elective PCI of left anterior descending, right coronary artery and left main coronary artery. Subjects with a history of autoimmune disorders, collagen disease, uncontrolled hypertension, diabetes mellitus, left ventricular dysfunction with an ejection fraction <35%, heart failure, congenital heart disease, arrhythmias, valvular heart disease, neuropsychiatric disorders, and other medical comorbidities were excluded from the study.

### Study design

Heart rate variability analysis: All subjects were invited to the autonomic function testing laboratory in the Department of Physiology, VMMC and Safdarjung hospital, New Delhi, India. The protocol of HRV analysis was explained to them beforehand. On the day of testing, the subjects were instructed

to lie down in the supine position. The electrodes for recording the electrocardiogram (ECG) in lead II were placed and the subjects were allowed to rest for 10-15 minutes, then the ECG was recorded for five minutes. Subjects were instructed to close their eyes throughout the procedure and to avoid activities such as talking, movement of the body, coughing and sleeping. Both time and frequency domain parameters were determined.

**Time domain analysis:** The parameters recorded by time-domain analysis were mean heart rate, standard deviation of all R-R intervals (SDNN), square root of mean squared differences of successive NN intervals (RMSSD), number of intervals differing by >50ms from the adjacent interval (NN50) and percentage of NN50 (pNN50).

**Frequency domain analysis:** This analysis was performed using a nonparametric method of fast Fourier transform (FFT). The power spectrum was subsequently quantified into standard frequency-domain measurements as defined previously,<sup>10</sup> including total power (TP), low frequency (LF) (0.04-0.15 Hz), high frequency (HF) (0.15-0.40 Hz) and LF:HF ratio. The 0.15-0.4 Hz band of R-R power, which is considered as HF, reflects parasympathetic nerve activity on the heart, whereas 0.04-0.15 Hz, which is considered as LF, represents sympathetic activity. The ratio of LF:HF represents sympathovagal balance<sup>11</sup>.

### Statistical analysis

The data were compiled and entered in MS Excel and analysed using the licensed statistical software: SPSS version 21.0. The values were expressed as mean±standard deviation (SD). Statistical significance of the differences between pre-post interventions were carried out using paired Student's t-test or nonparametric tests. Multivariate analyses were done using regression analysis and Pearson's correlation coefficient. The significance level was considered as p<0.05.

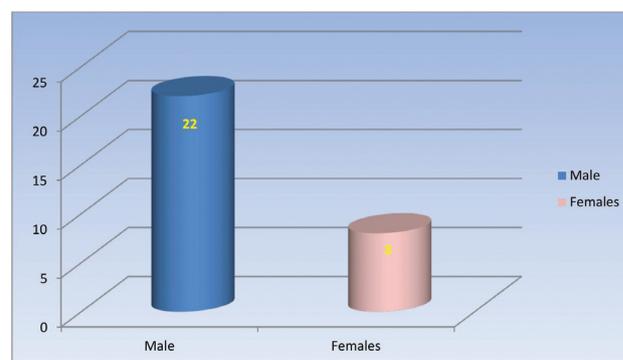
## RESULTS

The present study included 30 PCI candidates with CSA aged 45-70 years. Table 1 shows the basic characteristics of all subjects. The age of the CSA patients was 53.7±8.9 years. Regarding gender distribution, study population consisted of 22 men (73.3%) and 8 women (26.67%), as shown in Figure 1. The mean age of the women was 51.25±10.81 and that of the men was 54.29±8.376 years. Body mass index of the subjects was found to be 24.23±2.59 kg/m<sup>2</sup>.

**Table 1. Basal characteristics of chronic stable angina patients.**

Parameters	(n=30)
Age (yrs)	53.7±8.9
Male	22 (73.3%)
Female	8 (26.67%)
BMI kg/m <sup>2</sup>	24.23±2.59
History of diabetes	3 (10%)
History of hypertension	5 (16.66%)
History of hypertension & diabetes	14 (46.66%)
Smokers	17 (56.66%)
Smokers+alcoholics	4 (13.33%)
Duration of CSA (months)	7.56±5.05

Values are expressed as mean±SD or number (%). BMI-body mass index; n-number; CSA-Chronic stable angina.



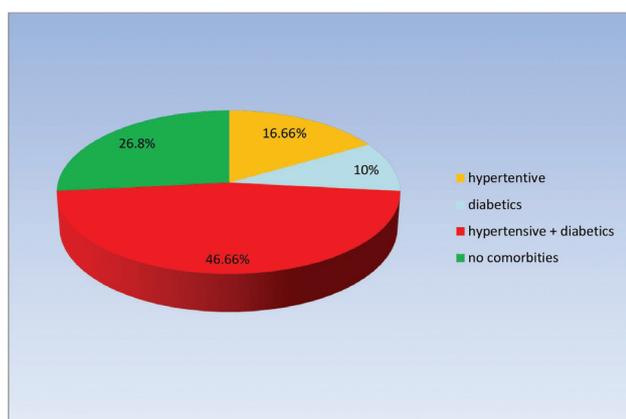
**Figure 1. Comparison of gender distribution in chronic stable angina patients.**

Males were more as compared to females.

Regarding the presence of comorbidities in the CSA patients, three (10%) cases were diabetic, five (16.66%) hypertensive and 14 (46.66%) both diabetic and hypertensive. Furthermore, 17 (56.66%) patients had a history of smoking and four (13.33%)

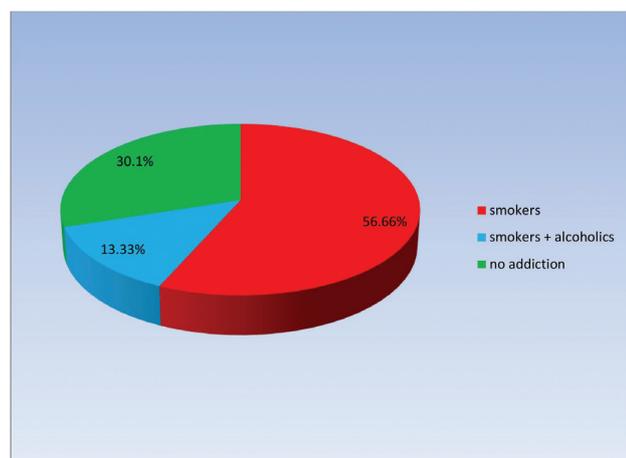
had a history of both smoking and alcoholism, (Figure 2). The mean duration of stable angina was  $7.56 \pm 5.05$  months. The time-domain parameters of SDNN ( $61.47 \pm 22.27$  vs.  $32.24 \pm 16.50$ ms,  $p < 0.0001$ ), RMSSD ( $53.86 \pm 31.41$ ms vs.  $28.81 \pm 23.80$ ms,  $p = 0.001$ ), and pNN50 ( $46.24 \pm 34.36$  vs.  $5.20 \pm 6.63$ ,  $p < 0.0001$ ) in post-PCI were significantly higher when compared with the pre-PCI values (Figure 4 and Table 2). There were significant increases in both post-PCI LF ( $1054.60 \text{ms}^2 \pm 208 \text{ms}^2$  vs.  $1193 \pm 302.04 \text{ms}^2$ ,

$p < 0.001$ ) and HF ( $991.57 \text{ms}^2 \pm 872.40 \text{ms}^2$  vs.  $466.72 \text{ms}^2 \pm 257.93 \text{ms}^2$ ,  $p < 0.0001$ ) when compared with the pre-PCI values (Table 3 and Figure 5). Post-PCI TP was significantly increased as compared to pre-PCI ( $3548.37 \pm 2428.58 \text{ms}^2$  vs.  $807.73 \pm 867.07 \text{ms}^2$ ,  $p < 0.0001$ ). The LF:HF ratio in pre-PCI was higher as compared to post-PCI ( $1.467 \pm 1.639$  vs.  $1.143 \pm 0.852$ ,  $p = 0.805$ ), but the intergroup difference was not statistically significant (Table 3 and Figure 6).



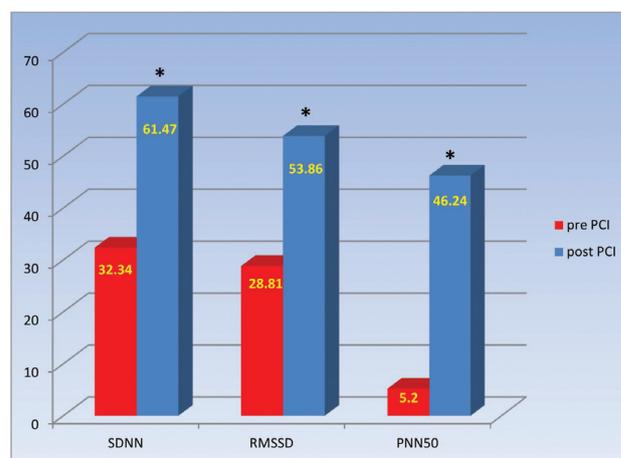
**Figure 2. Distributions of co morbidities in patients of chronic stable angina.**

46.66% patients were having both Hypertension and Diabetes, 16% patients were hypertensives 10% patients were Diabetics and 26.8% patients had no comorbidities.



**Figure 3. Distributions of history of addiction in patients of chronic stable angina.**

13.33% patients were both smokers and alcoholics, 56.66% patients were smokers and patients had no addiction.



**Figure 4. Comparison of Time domain parameters in chronic stable angina patients pre and post Percutaneous Coronary Intervention (PCI).**

SDNN-standard deviation of the normal-to-normal R-to-R interval; RMSSD-square root of mean squared differences of successive NN intervals; Post PCI showed significant improvement in SDNN, RMSSD and PNN50 as compared to Pre PCI.

\*p value <0.05, statistically significant.

**Table 2. Comparison of time domain parameters of heart rate variability in chronic stable angina patients pre and post Percutaneous Coronary Intervention (PCI).**

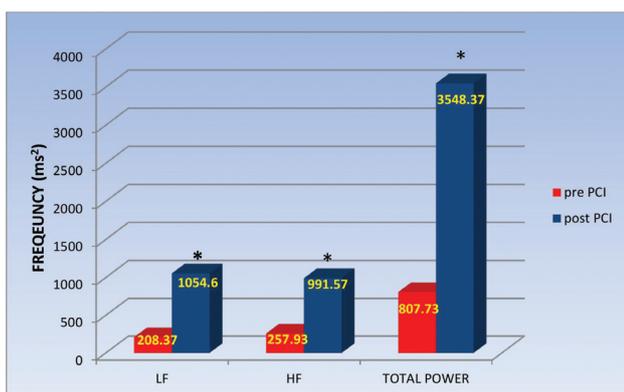
Parameters	Pre-PCI (n=30) Mean±SD	Post-PCI (n=30) Mean±SD	p Value
SDNN (ms)	32.24±16.50	61.47±22.27	<0.0001
RMSSD (ms)	28.81±23.80	53.86±31.41	0.001
pNN50 (%)	5.20±6.63	46.24±34.36	<0.0001

Values are expressed as mean±SD or number (%). BMI-body mass index; n-number; CSA-Chronic stable angina.

**Table 3. Comparison of frequency domain parameters in chronic stable angina patients pre and post Percutaneous Coronary Intervention (PCI).**

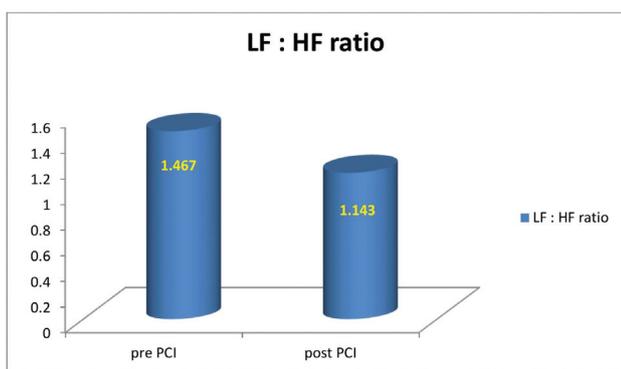
Parameters	Pre-PCI (n=30) Mean±SD	Post-PCI (n=30) Mean±SD	p Value
LF (ms <sup>2</sup> )	1193±302.04	1054.60±208	<0.001
HF (ms <sup>2</sup> )	466.72±257.93	991.57±872.40	<0.0001
LF/HF	1.467±1.639	1.143±0.852	0.805
Total Power (ms <sup>2</sup> )	2428±867.07	3548.37±807.73	<0.0001

HRV-heart rate variability; LF-low frequency; HF-high frequency; LF/HF-ratio; ms<sup>2</sup> - millisecond squared; p value<0.05 statistically significant.



**Figure 5. Comparison of frequency domain parameters in chronic stable angina patients pre and post Percutaneous Coronary Intervention (PCI).**

LF-low frequency; HF-high frequency; \*p value<0.05, statistically significant. Post PCI showed significant improvement in LF, HF and Total power as compared to Pre PCI.



**Figure 6. Comparison of LF/HF ratio (low frequency to high frequency ratio) in chronic stable angina patients pre and post. Percutaneous Coronary Intervention (PCI).**

Post PCI showed lower LF:HF ratio as compared to Pre PCI

## DISCUSSION

In this study, the pre-PCI time-domain parameters, such as SDNN ( $p<0.0001$ ), RMSSD ( $p<0.0001$ ), and pNN50 ( $p<0.0001$ ) in the CSA patients were significantly lower than the post-PCI values of these parameters.

Frequency-domain parameters such as LF, HF, and TP were also significantly lower in the pre-PCI patients when compared with the post-PCI patients. Though not statistically significant a decrease in LF:HF ratio was observed in the post-PCI patients. Reduced SDNN, RMSSD, pNN50, HF, and TP indicate a reduced HRV characterized by an imbalance between the parasympathetic and sympathetic systems and reduced parasympathetic activity. However, a significantly reduced LF implies a reduction in sympathetic activity as well. Thus, our HRV findings reflect autonomic deficit in the pre-PCI patients, with a predominant loss of parasympathetic tone. It is known that HRV exhibits autonomic responses to environmental and external stimuli, which in turn indicate the sympathetic and parasympathetic effects on the heart<sup>12</sup>. HRV analyses provide crucial information about the balance between the sympathetic and parasympathetic influences on the pacemaker of the heart; i.e., the sinoatrial node and its intrinsic rhythm<sup>13</sup>. In a healthy heart, both autonomic nervous system and sinoatrial node are able to respond dynamically to different environmental challenges, thereby resulting in increased HRV. On the other hand, a decreased responsiveness of the autonomic nervous system or the sinoatrial node to a change results in reduced HRV<sup>14</sup>. Our finding of decrease in HRV parameters in the CSA patients pre-PCI is in accordance with earlier studies and signifies sympathetic predominance and a concomitant parasympathetic deficit in the pre-PCI CSA patients. Pivatelli et al.<sup>15</sup> found reduced parasympathetic activity in patients suffering from coronary artery disease with decrease in HF, RMSSD, and NN50; and they stated that these

parameters could be used as prognostic markers in patients with CSA.

Partly similar to our findings, a study by Aydinlar et al.<sup>16</sup> also showed that the components of HF, RMMSD, and SDNN were significantly increased whereas LF and LF:HF ratio were significantly reduced after PCI. We observed, though not statistically significant, an increase in LF and a reduction in LF:HF ratio in the post-PCI subjects. According to some reports, the LF spectral component of HRV represents sympathetic nervous activity, whereas others believe it to be the result of both sympathetic and vagal influences<sup>11</sup>. Abrootan et al.<sup>17</sup> studied the changes in HRV indices after PCI, and observed an increase in post-PCI SDNN. Contrary to our results, Kanadasi et al.<sup>18</sup> showed that revascularisation of definitive coronary obstruction by PCI has no beneficial effect on vagal regulation of the heart rate. The possible explanation for a state of sympathetic predominance with reduced parasympathetic component in pre-PCI CSA patients and its reversal following revascularisation by PCI could be the activation of several neural responses by occlusion of the coronary vessels. Some of these responses are triggered by the stimulation of mechanoreceptors in coronary circulation. Others are induced by the stimulation of the mechanoreceptors and chemoreceptors in the ventricular wall, and the activation of these ventricular receptors is mainly due to the occlusion of the coronary vessels, and thus, myocardial ischemia<sup>16</sup>. Increase in coronary blood flow as well as mechanical stretch are known to result in the stimulation of the mechanoreceptors situated in the left coronary artery which may induce a reflex decrease in the sympathetic drive<sup>16</sup>. Contrarily, occlusion of the left coronary artery experimentally results in the stimulation of mechanoreceptors and chemoreceptors present in the ventricular wall, and this stimulation increases the activity of the sympathetic efferent axons that extend towards the heart<sup>16</sup>.

Abdelnaby et al.<sup>19</sup> demonstrated that dysfunction of the segmental part of the left ventricle was involved in the imbalance of the sympathovagal system in patients with CSS and that intervention by PCI improved the HRV and the left ventricular dysfunction. These findings support the hypothesis that if cardiac functioning is altered, it leads to the discharge of afferent sympathetic mechanoreceptors, thus causing dysfunction in the autonomic control of the heart rate. The researchers also found increases in post-PCI SDNN, RMSSD, pNN50, LF, and HF. These findings are similar to the observations of the present study.

In patients with single vessel CCS, apart from the dysfunction of the left ventricle, stress indices of the systolic and diastolic wall determine the imbalance of the sympathovagal system synergistically. When the left ventricular dysfunction is reversed, the indices of wall stress improve the HRV. Alterations in cardiac functioning and ventricular wall stress mainly lead to the discharge of efferent vagal and afferent sympathetic innervations, thus modulating the long-term instead of short-term heart rate fluctuations<sup>8</sup>.

Similar to our findings, another study by Sedziwy et al.<sup>20</sup> on the HRV time-domain parameters in pre-PCI and post-PCI patients, concluded that there were significant improvements in HRV, indicating the restoration of the autonomic balance by successful revascularization.

## CONCLUSION

On the basis of our preliminary results, it may be concluded that autonomic dysfunction is present in patients with CSA pre-PCI, and after revascularization procedures such as PCI that significantly improves cardiac autonomic functions. These findings signify improvements in both basal cardiac autonomic tone and autonomic reactivity in patients with CSA.

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