Abstract. – OBJECTIVE: The objective of this study is to investigate the relationship and predictive power between heart rate variability (HRV) and radial artery spasm, in cases where the radial artery is preferred as the access route for coronary angiography (CAG).

PATIENTS AND METHODS: A total of 394 patients, who were scheduled to have CAG were included in this study. Patients who developed radial artery spasms during CAG, performed using the radial artery as the access route, were analyzed for HRV parameters.

RESULTS: Ages of the patients ranged between 31 and 74 years. Significant time domain measurements such as the standard deviation of normal-normal (NN) intervals, the standard deviation of the averages of NN, the average of the standard deviations of all NN intervals, and root mean square of successive differences between normal heartbeats were statistically significantly lower in the patient group that developed radial artery spasm. Frequency field measurements with prognostic values such as HF (high frequency) and very low frequency were also statistically significantly lower in the patient group that developed radial artery spasms. On the other hand, there was no statistical difference between the groups in LF (low frequency) and LF/HF ratio measurements. A statistically significantly higher radial artery spasm rate was observed in the coexistence of anxiety and low HRV.

CONCLUSIONS: A significant decrease was found in major HRV values, which are closely related to the autonomic nervous system and its dysfunction, in patients with radial artery spasms.

Key Words: Autonomic dysfunction, Radial artery spasm, Heart rate variability, Coronary angiography, Holter electrocardiography.

Introduction

Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats and is one of the most promising non-invasive diagnostic methods for assessing autonomic dysfunction. HRV may also be interpreted as the speed differences of the heart from beat to beat. It is closely related to the function of the sympathetic and parasympathetic nervous systems, that is, the autonomic nervous systems, which have a common effect on the work of the heart, albeit to a different extent. Hence, HRV provides important insight into autonomic regulation and HRV measurement can efficiently reflect the activity of both sympathetic and vagal components of the autonomic nervous system on the sinus node of the heart. HRV values have been implicated as independent and strong predictors of mortality in some specific groups of cardiac patients. One of the acknowledged methods of assessing the cardiovascular risk and efficiency of the autonomic nervous system is the measurement of HRV and heart rate turbulence (HRT)2,3.

Recently, the radial artery has been increasingly preferred as an access route in coronary catheterization with a view to reducing bleeding complications4. Current guidelines strongly recommend the use of radial artery as an access route for coronary interventions5. The use of radial arteries is even more pronounced in cases where multiple anticoagulants should be used. The increasing use of radial arteries in coronary interventions has translated into a significant reduction in vascular complications in clinical practice worldwide6. However, radial artery spasm, along with radial artery occlusion as adverse events associated with the use of ra-
dial arteries in coronary interventions, seem to limit further use of radial arteries by operators. A report published in 2004 indicated that severe spasms occurred in over 50% of patients that received trans-radial catheterization and that its incidence was inversely correlated with arterial diameter. On the other hand, lower rates have been reported in more recent studies, which can be attributed to the increasing experience and developing technology in the relevant field. Nevertheless, the rates of radial artery spasms reported in studies still vary greatly. This may be attributed to a combination of factors, including sheath size, vessel size, procedural differences, the experience of the interventionalist, and different definitions of spasm.

The relationship of HRV, which is associated with the autonomic nervous system, with mortality in the context of coronary artery disease, as well as with sinus node activity and many neurological and psychiatric conditions has been investigated in many studies. There are studies available in the literature in which autonomic function was evaluated in patients that underwent percutaneous coronary intervention. However, to date, the relationship between these two conditions, both of which are related to the autonomic nervous system, has not been evaluated sufficiently in the literature. The physiological and pathophysiological processes of the autonomic nervous system on these two parameters are clear. In view of the foregoing, the aim of this study is to evaluate the relationship of HRV, a parameter related to autonomic nervous system function, with radial artery spasm, which is the result of the same nervous system activity and appears to be the most prominent problem when it is preferred as the access route in coronary angiography and to assess the potential power of HRV in predicting the radial artery spasm.

**Patients and Methods**

**Population and Sample**

The population of the study comprised 486 patients admitted to the clinic where this study was conducted with the diagnosis of stable angina pectoris between June 2017 and July 2018. Of these patients, patients with supraventricular or ventricular arrhythmia (n:3), pacemaker (n:7), severe heart valve disease (n:6), chronic kidney failure (n:9), liver disease (n:5), patients who were in atrial fibrillation rhythm or who had paroxysmal atrial fibrillation attacks for more than 6 seconds (n:21), patients with the excessive artifact in 24-hour rhythm Holter recording (n:11), Holter recording less than 22 hours (n:8), patients who had frequent (over 10% in 24 hours) ventricular extrasystolic attacks (n:11), patients with a history of cerebrovascular disease (n:2), patients diagnosed with peripheral artery disease (n:2), professional athletes (n:3), and those who did not consent to participate in the study (n:3) were excluded from the study. All in all, 394 patients who were scheduled for coronary angiography, whose 24-hour Holter ECG recordings were taken beforehand, and who met the study inclusion criteria were included in the study as the study group.

The study protocol was approved by the local ethics committee (No. 78017789-050.01.04/E.909014) and was carried out in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

The baseline demographic characteristics of all patients were recorded. Venous blood samples were taken from the patients after at least 8 hours of fasting, and their biochemical and hematological tests were conducted using standard laboratory techniques.

The Hamilton Anxiety Rating Scale (HAM-A), which consists of 14 items, was used to determine the anxiety scores of all patients included in the study. The results were recorded as scoring.

**Electrocardiographic Analyses**

12-lead surface electrocardiography (ECG) (GE Marquette MAC2000, 2063587-001; Ventura, CA, USA) was performed on all patients in a supine position at a rate of 25 mm/ms and 10 mV/sec.

**24-Hour Holter Monitoring and Heart Rate Variability Measurements**

Heart rhythms of all patients were analyzed via 24-hour Holter Monitoring (SEER TM 1000 SN 391 16 05290; Mississauga, ON, Canada) within the last 120 hours before they had coronary angiography. The recordings were made in accordance with the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, and interpreted separately by two cardiologists. Prominent R waves were taken as a reference while measuring HRV. Computerized HRV measurements were taken as a basis by configuring
the normal-normal (NN) R intervals in the image file created via the data processing program in the Holter recording17,18.

In time-based HRV measurements, the interval (NN interval) between two adjacent R waves is measured for the duration of the Holter recording. The standard deviation of NN (SDNN) is called the standard deviation of all NN (RR) intervals over the 24-hour Holter recording and is the most commonly used measure among the time-based measurements18. Standard deviation of the averages of NN (SDANN) is the standard deviation of the averages of NN intervals in all 5-minute segments of a 24-hour Holter recording, average of the standard deviations of all NN intervals (ASDNN) is the mean of the standard deviations of all NN intervals for all 5-minute segments in the 24-hour Holter recording. Root mean square of successive differences (rMSSD) between normal heartbeats is the root of the mean of squares of the differences between consecutive NN intervals. pNN50 is the ratio of the number of pairs of successive NN intervals that differ by more than 50 ms from the previous interval compared to the total number of NN intervals. Other measures include SDNNI (SDNN Index), which is the mean of the standard deviations of all the NN intervals for each 5 min segment of the 24-hour Holter recording, and HRV triangular index, which is the total number of all NN intervals divided by the height of the histogram of all NN intervals19.

In spectral or frequency-based HRV measurements, the output consisting of 5 frequency bands ranging from 0 to 0.5 Hz is calculated using spectral density analysis. The low-frequency (LF), mid-frequency (MF) and high-frequency (HF) bands account for only 5% of the total output. HF is considered a measure of isolated parasympathetic activity. LF, on the other hand, is considered a measure of predominantly sympathetic activity modulated by the action of the parasympathetic system. The ultra-low frequency (ULF) and very low frequency (VLF) bands, which make up most of the total output, have much less resolution than the output generated by the HF and LF bands20,21.

**Coronary Angiography**

Coronary angiography was performed with the GE Optima IGS 320 device (Chicago, IL, USA) via the Judkins technique using a diagnostic 6F Judkins catheter. A 6F Judkins procedural catheter was used in patients who underwent percutaneous coronary intervention. The mixture containing nitroglycerin, as the vasodilator agent, and verapamil was routinely administered to all patients. The Allen test was performed on all patients. All operations were carried out by the same operator. Patients who had to undergo 4 or more puncture attempts during radial puncture were excluded from the study.

A diagnosis of radial artery spasm was made in the event of difficulty of catheter manipulation, feeling of pain, and angiographic evidence.

**Statistical Analysis**

The collected data were recorded in the SPSS 20.0 (Statistical Package for Social Sciences for Windows, version 20.0, IBM Corp., Armonk, NY, USA) software package. The Kolmogorov-Smirnov test was used to determine whether the data conform to normal distribution or not. Among the data that was determined to conform to the normal distribution, numerical variables were expressed as mean ± standard deviation values, whereas categorical variables were expressed as percentage (%) values. Student’s t-test and Pearson’s Chi-squared test were used to compare the numerical and categorical variables that were determined to conform to the normal distribution, respectively, between any two groups. The data that were determined not to conform to normal distribution were expressed as median (minimum-maximum) values and the Mann-Whitney U test was used for their comparisons between any two groups. Multivariate logistic regression analysis was conducted using the parameters with probability p-values lower than 0.01 to identify the independent predictors of radial artery spasm. p-values of < 0.05 were deemed to indicate statistical significance.

**Results**

The mean age of the 394 patients included in the study was 52.55 ± 9.32 (min 31, max 74) years. Of these patients, 199 (50.5%) were female. There was no significant difference between the groups of patients who did and did not develop radial artery spasms in terms of age and gender (p:0.089 and p:0.127, respectively). There was also no significant difference between the two groups in terms of smoking history, presence of diabetes, hypertension, and hyperlipidemia, and use of oral antidiabetics, insulin, nitrates, beta-blockers, calcium channel blockers and ACE (angiotensin-converting enzyme) inhibitors (Table I).
6F Judkins catheter was used for diagnostic purposes in patients who underwent coronary angiography procedure, whereas 6F Judkins procedural catheter was used in patients who underwent percutaneous coronary intervention. There was no statistically significant difference between the groups of patients who did and did not develop radial artery spasms in terms of the number of catheter use, total angiography time, the number of patients who underwent percutaneous coronary intervention, and the amount of contrast. As for the results of the laboratory tests, there was also no significant difference between the said two groups in terms of creatinine values and HbA1c (glycosylated hemoglobin) rates. The mean SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score of the group of patients who developed radial artery spasm was higher than the other group, albeit not statistically significant (p:0.676).

The comparison of the mean values of HRV parameters between the groups of patients who did and did not develop radial artery spasms revealed significant differences in most parameters. Accordingly, from among the frequency parameters, the VLF and HF rates were found to be significantly lower in the group of patients who developed radial artery spasm than the other group (p<0.001, 95% confidence interval [CI] 0.777-0.921) were a predictor of radial artery spasm independently of all other parameters (Table III).

Discussion

The main finding of this study is that the HRV parameters, i.e., NN, SDNN, SDANN, RMSSD, and pNN50 values, evaluated before the procedure, were found to be significantly lower in the group of patients who developed radial artery spasms than the other group (Table II). Additionally, the mean HAM-A score of the group of patients who developed radial artery spasm was significantly higher than the other group (p:0.042).

A detailed logistic analysis of the statistically significant decreases observed in HRV parameters in the group of patients who developed radial artery spasm revealed that low VLF values (p<0.001, 95% confidence interval [CI] 0.777-0.921) were a predictor of radial artery spasm independently of all other parameters (Table III).
On the other hand, confounding results were obtained in LF and LF/HF ratio measurements. Lastly, the finding of the seemingly synergistic effect of low HRV values on radial artery spasms in anxiety patients is another important result of this study.

Time domain parameters, i.e., NN, SDNN, SDANN, and rMSSD, constitute the main components of clinical HRV assessments. Different pathologies have been investigated in many studies by means of these parameters. To give a few examples, Yang et al. reported that these parameters were important predictors of mortality after acute coronary syndrome. Sessa et al. demonstrated that low HRV values were associated with sudden cardiac death in patients with acute myocardial infarction and heart failure. Alauddin et al. found that low SDNN,

Table II. Demographics and comparison of HRV parameters.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient group without radial artery spasm (n: 321)</th>
<th>Patient group with radial artery spasm (n: 73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.92 ± 9.41</td>
<td>50.93 ± 8.84</td>
<td>0.089</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.32 ± 7.52</td>
<td>78.66 ± 8.31</td>
<td>0.096</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182.36 ± 126.69</td>
<td>171.01 ± 5.96</td>
<td>0.445</td>
</tr>
<tr>
<td>Total angiography time (minutes)</td>
<td>16.99 ± 5.78</td>
<td>18.34 ± 5.38</td>
<td>0.068</td>
</tr>
<tr>
<td>Contrast amount (mL)</td>
<td>91.59 ± 44.74</td>
<td>98.08 ± 43.26</td>
<td>0.261</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>5.18 ± 6.65</td>
<td>4.81 ± 7.42</td>
<td>0.676</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>76.93 ± 19.45</td>
<td>74.27 ± 13.26</td>
<td>0.351</td>
</tr>
<tr>
<td>HbA1c (glycosylated hemoglobin) (mmol/mol)</td>
<td>5.98 ± 0.77</td>
<td>6.15 ± 0.90</td>
<td>0.086</td>
</tr>
<tr>
<td>Very low frequency (VLF)</td>
<td>35.10 ± 12.59</td>
<td>22.98 ± 7.18</td>
<td>0.000</td>
</tr>
<tr>
<td>Low frequency (LF)</td>
<td>36.06 ± 9.38</td>
<td>27.81 ± 6.94</td>
<td>0.068</td>
</tr>
<tr>
<td>High frequency (HF)</td>
<td>16.37 ± 6.71</td>
<td>10.41 ± 3.77</td>
<td>0.000</td>
</tr>
<tr>
<td>Low/high (LF/HF)</td>
<td>1.68 ± 0.34</td>
<td>1.71 ± 0.29</td>
<td>0.542</td>
</tr>
<tr>
<td>SDNN</td>
<td>122.00 ± 24.25</td>
<td>102.41 ± 23.07</td>
<td>0.000</td>
</tr>
<tr>
<td>SDANN</td>
<td>101.08 ± 25.11</td>
<td>85.29 ± 24.83</td>
<td>0.000</td>
</tr>
<tr>
<td>mSSD</td>
<td>63.35 ± 16.16</td>
<td>46.51 ± 12.84</td>
<td>0.000</td>
</tr>
<tr>
<td>rMSSD</td>
<td>34.31 ± 9.99</td>
<td>25.77 ± 7.41</td>
<td>0.000</td>
</tr>
<tr>
<td>pNN50</td>
<td>10.81 ± 6.40</td>
<td>7.83 ± 4.51</td>
<td>0.000</td>
</tr>
<tr>
<td>Hamilton Anxiety Rating Scale (HAM-A) score</td>
<td>14.62 ± 4.87</td>
<td>17.34 ± 5.12</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Table III. Logistic analysis of HRV parameters in group of radial artery spasm.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p-value</th>
<th>95% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>VLF</td>
<td>-0.168</td>
<td>0.043</td>
<td>14.986</td>
<td>1</td>
<td>0.000</td>
<td>0.777</td>
</tr>
<tr>
<td>HF</td>
<td>0.041</td>
<td>0.076</td>
<td>0.298</td>
<td>1</td>
<td>0.585</td>
<td>0.898</td>
</tr>
<tr>
<td>SDNN</td>
<td>0.023</td>
<td>0.025</td>
<td>0.786</td>
<td>1</td>
<td>0.375</td>
<td>0.973</td>
</tr>
<tr>
<td>SDANN</td>
<td>-0.013</td>
<td>0.021</td>
<td>0.422</td>
<td>1</td>
<td>0.516</td>
<td>0.948</td>
</tr>
<tr>
<td>ASDNN</td>
<td>-0.040</td>
<td>0.021</td>
<td>3.499</td>
<td>1</td>
<td>0.061</td>
<td>0.921</td>
</tr>
<tr>
<td>RMSSD</td>
<td>-0.051</td>
<td>0.035</td>
<td>2.120</td>
<td>1</td>
<td>0.145</td>
<td>0.887</td>
</tr>
<tr>
<td>pNN50</td>
<td>-0.111</td>
<td>0.193</td>
<td>0.328</td>
<td>1</td>
<td>0.567</td>
<td>0.613</td>
</tr>
</tbody>
</table>

HRV, heart rate variability; SE, standard error; CI, confidence interval; EXP(B), exponentiation of the B coefficient; VLF, very low frequency; HF, high frequency; SDNN, the standard deviation of NN intervals; SDANN, standard deviation of the averages of NN; ASDNN, average of the standard deviations of all NN intervals; rMSSD, root mean square of successive differences between normal heartbeats; pNN50, ratio of number of pairs of successive NN intervals that differ by more than 50 ms from the previous interval compared to the total number of NN intervals.
LF is closely related to baroreceptor activity. LF is closely related to baroreceptor activity. LF is closely related to baroreceptor activity. LF contains both sympathetic and parasympathetic components, whereas HF is mainly associated with parasympathetic activity, and LF/HF ratio is associated with the balance between the sympathetic and parasympathetic activities. From this point of view, it can be said that the complicated SNS and PNS relationship cannot be clearly explained with these data. Therefore, evaluation of HF is more likely to give results that can be interpreted, as was the case in this study.

Inazumi et al. investigated autonomic nerve activity in patients with variant angina. These results are in agreement with the changes in HRV parameters. As also demonstrated in the literature, the relationship between the VLF measurements and the renin-angiotensin system carries this parameter to a different dimension in terms of cardiology. As a matter of fact, low levels of VLF were found to be associated with arrhythmic deaths and high inflammation. Although these relationships are not established, the high atherosclerotic risk may suggest endothelial problems.

In this study, the VLF, which is one of the major parameters in many respects, was found to be significantly lower in the group of patients who developed radial artery spasms. Moreover, further logistic regression analysis of the change in VLF in the said patient group indicated that it was, in fact, the most significant change.

The relationship between low HRV parameters, anxiety, and psychiatric disorders has been investigated in many studies, and generally lower HRV values were found to be associated with worse prognosis and outcomes. In one of these studies, Kirsanski et al. reported that HRV was a significant biomarker of antidepressant drug response and that higher HRV values were associat-
Radial artery spasm and heart rate variability

Radial artery spasm and heart rate variability

ed with better outcomes in the context of anxious depression, particularly compared to nonanxious depression. Thayer et al. demonstrated that patients with generalized anxiety disorder have lower HRV values. Additionally, Ercan et al. reported a significant relationship between higher anxiety levels and more severe radial spasms, especially in female patients. Similarly, in this study, radial artery spasm was significantly more common among the patients with low HRV values and patients with high anxiety scores. Anxiety is one of the aggravating factors that increase the risk of cardiovascular mortality. Anxiety patients have both low HRV values and increased radial artery spasm. In parallel, in this study as well, the radial spasm was found to be more common in patients with low HRV values. From this point of view, the seemingly synergistic relationship between anxiety, HRV, and radial artery spasm is noteworthy.

It has been reported in the literature that time domain parameter values in particular decrease with age. This decrease in the values of time domain parameters with age was explained by Nicolini et al. with the tendency to decrease in respiratory sinus arrhythmia with age. It has also been reported in the literature that radial artery tortuosity increases with increasing age due to the effect of certain disorders such as hypertension. Radial artery tortuosity, which may predispose to a more difficult puncture, painful puncture, or failure in the first puncture, may increase the risk of radial artery spasm. In addition, higher body mass index (BMI) values were found to be associated with a higher risk of radial artery spasm and lower HRV values. Furthermore, it was also reported that the use of beta-blockers, ACE inhibitors, calcium channel blockers, or digoxin affected the results of HRV measurements. Nevertheless, in this study, no significant difference was found between the groups of patients who did and did not develop radial artery spasms in terms of any of the demographic and clinical parameters mentioned above including age, BMI, medications used, and HT.

Additionally, it has been reported in the literature that patients with type 2 diabetes mellitus (DM) have lower HRV values. In comparison, in this study, a higher rate of patients who developed radial artery spasms had DM diagnosis and high glycosylated hemoglobin (HbA1c) levels as compared to patients who did not develop radial artery spasms, albeit not statistically significantly.

Lastly, it has also been reported in the literature that the radial artery spasm rate increases as the duration of angiography increases in interventions performed through the radial artery. However, in this study, the analysis of the total angiography times of the groups of patients who did and did not develop radial artery spasms did not reveal any statistical difference between the groups.

Conclusions

The findings of this study suggest that HRV parameters can be used in predicting the radial artery spasm which may arise as a complication in cases where the radial artery is preferred as the site of intervention in patients with stable angina pectoris. Particularly, in combination with the time and frequency domain parameters associated with 24-hour Holter monitoring, which have proven high prognostic values. In this study, a significantly higher number of patients with low SDNN, SDANN, rMSSD, and pNN50 values, which are among the major HRV parameters considered indicators of autonomic dysfunction, had radial artery spasms. Additionally, the relationship found between the HF and VLF values, which are among the major frequency parameters, and the presence of radial artery spasm is also noteworthy. Although the effort to explain the complex sympathetic-parasympathetic nervous system relationship with HRV measurements alone may seem confounding, the relationship between HRV measurements and many clinical conditions can be demonstrated. Further large-scale studies are needed to verify the predictive power of HRV parameters in predicting radial artery spasms demonstrated in this study.

Conflict of Interest

The authors have no potential conflict of interest to declare concerning this paper.

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The study received no funding.
Authors’ Contribution
All authors contributed to the following: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Data Availability Statement
The data of the study will be shared with those who want to access the data.

Ethics Statement
The study protocol was approved by the Local Ethics Committee (N°78017739-050.01.04/E.909014) and was carried out in accordance with the principles outlined in the Declaration of Helsinki. This project received institutional review board approval from Mersin University Institutional Review Board and the Ethics Committee.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

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