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Heart rate variability in patients presenting with anginal symptoms in absence of cardiac and other diseases

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ABSTRACT

Objectives: Angina is a symptom of coronary artery disease (CAD). Modulation of cardiac autonomic tone as assessed by heart rate (HR) variability (HRV) is found reduced in patients with CAD; myocardial ischemia, myocardial infarction and some other cardiovascular diseases. Reduced HRV has been found associated with sudden cardiac death in these CAD patients. Several patients present with anginal symptoms clinically in absence of CAD or other diseases. The status of HRV is not much clear in these patients. Thus, we aimed to assess HRV in patients with angina with and without myocardial ischemia and compare it with HRV of healthy subjects of similar age groups and follow-up patients for 1 year for cardiac/health events.

Materials and Methods: The study included 61 consecutive male patients clinically presenting with angina and 30 healthy subjects. Based on Thallium-201 myocardial perfusion Single-photon emission computerized tomography (SPECT) imaging, patients were divided into two groups; patients with myocardial perfusion defects (MPD), (n = 33, age 54.91 ± 7.43 years) and patients with no MPD (NMPD), NMPD (n = 28, age 53.04 ± 8.50 years). Short-term HRV was assessed in all patients and subjects in resting supine position following standard protocol. All MPD and 25 NMPD patients could be followed up for 1 year for cardiac/health events.

Results: Surprisingly, the NMPD patients showed significantly reduced HRV, Standard deviation of the N-N intervals, The square root of the mean squared differences of successive N-N intervals, Percentage of the number of interval differences of successive N-N intervals greater than >50 ms divided by total number of R-R intervals, low frequency (LF) power, High Frequency (HF) power and total power as compared to both MPD patients and healthy subjects. (Total power [NMPD vs. MPD]: 610.1 [379.9–1072.8] vs. 1508.0 [748.4–2339.4] millisecond squares (ms^2), P = 0.001), healthy subjects (Total power: 1414.6 [1104.6-2141.5] ms^2, P = 0.001). The markers of sympathetic tone; LF (normalised unit) and LF/HF ratio were higher in NMPD patients as compared to MPD patients resulting in an altered sympathovagal balance. During a 1-year follow-up, sudden death was seen in one MPD patient (3.1%) and two NMPD patients (8%).

Conclusion: The NMPD patients showed significantly reduced HRV as compared to both MPD patients and Healthy subjects with an altered sympathovagal balance. Sudden death was also seen in NMPD patients as MPD patients.

Keywords: Heart rate variability, Thallium-201, Anginal symptoms, Cardiac autonomic tone, Sudden death

INTRODUCTION

Angina is a symptom of coronary artery disease (CAD). It is a type of chest pain radiating to the left arm, basically developed due to reduced oxygen supply to the cardiac tissue. Modulation of cardiac autonomic tone as assessed by heart rate (HR) variability (HRV) is found reduced in patients with ischaemic heart diseases (IHD).[1-5]

The HRV is a non-invasive tool to assess beat-to-beat variations in the HR that is, the beat-to-beat variations in the R-R intervals. The beat-to-beat variations in HR are due to continuous changes in the sympathetic and parasympathetic outflow to the heart.[6] Therefore, HRV has become a reliable tool for the assessment of modulation of cardiac autonomic tone. The HRV was also found reduced in patients with uncomplicated CAD, particularly, vagal tone was found to be reduced.[2] Furthermore, a decrease in HRV, in patients with myocardial infarction (MI) was found to be associated with an increase in cardiovascular-related morbidity and mortality.[3,5,7]

Patients with IHD experience chest pain due to stimulation of cardiac spinal afferents by chemical adenosine and bradykinin released during ischaemia.[8] The pain may also occur in the shoulder, arm, neck, jaw or back. A set of investigations are performed to diagnose IHD cases following American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines,[9] which include blood investigations, 12-lead Electrocardiogram (ECG), treadmill test, thallium-201 myocardial perfusion SPECT imaging (Tl-201 MPI) and coronary angiography. The coronary angiography allows visualisation of the site and extent of occlusion. It is an invasive procedure. While the Tl-201 MPI is a non-invasive procedure. It is recommended as an investigation in patients with angina for the detection of myocardial ischemia.[9,10] The Tl-201 MPI demonstrated a high degree of accuracy in determination of presence, location and extent of IHD.[11-13] The Tl-201 MPI was also found to be sensitive for the detection of microvascular angina in patients with transient ST-segment elevation in treadmill tests and normal coronary angiography scans,[14,15] a reduced HRV was reported in these patients of microvascular angina.[16] Most of the published research showed that patients clinically presenting with angina whether they had myocardial ischaemia, MI or microvascular angina showed reduced HRV that is, reduced modulation of cardiac autonomic tone.

There are several patients who clinically present with symptoms like angina; however, on extensive investigations, they do not have any objective evidence of myocardial ischaemia or other known diseases. The status of HRV was not known in these patients with angina with no cardiac and other diseases. We found markedly reduced HRV and sudden death in a patient presenting with anginal symptoms in absence of cardiovascular and other diseases.[17] Thus, we aimed to assess short-term (HRV) in patients with angina with and without myocardial perfusion defects (MPD) and compared it with HRV of healthy subjects, and followed-up on all patients for 1 year for cardiac or other health-related problems.

MATERIALS AND METHODS

Participants

The study included 61 consecutive male patients presenting with angina, age 52.3 ± 7.9 years. All patients were referred from the department of cardiology of the institute after appropriate clinical and laboratory investigations. Patients with newly diagnosed or recurrent recent angina (≤2 months) were included in the study. They were on conventional therapy (Ecospirin, statins, nitrates, beta-blockers and calcium channel blockers).

Patients with unstable angina, MI (≤3.5 years), cardiac failure, bundle branch block, cardiomyopathy, frequent ventricular ectopics or other arrhythmias, uncontrolled hypertension, diabetes mellitus, chronic kidney diseases, chronic respiratory diseases, thyroid dysfunction and patients taking drugs other than conventional cardiac drugs, smokers and alcoholics were excluded from the study.

Thirty healthy subjects with no systemic diseases, non-smokers and non-alcoholics served as controls. They had normal ECG and normal cardiovascular autonomic functions as assessed by Ewings' battery of tests.[18]

The Ethics Committee of the institute approved the study and written informed consent was taken from all participants before their participation.

Study protocol

Short-term HRV of all patients was assessed in Autonomic Function Lab, Department of Physiology of the institute between 9:00 and 11:00 AM in a quiet room at room temperature 25 ± 1°C. Treatment of the patients was withheld before the test (β-blockers for 72 h, calcium channel blockers and other drugs for 24 h). Patients avoided tea and coffee for 24 h before the tests. A standardised proforma was used to record the history of patients, demographic profile and presence of any additional signs and symptoms.

All patients underwent stress-redistribution Tl-201 MPI in Nuclear cardiology Lab, Department of Nuclear Medicine of the institute after assessment of HRV on the same day for the assessment of myocardial perfusion. It was performed using standard protocol of stress-redistribution Tl-201 MPI.[19,20] All patients underwent an exercise protocol on treadmill. Images were acquired within 10–15-min post-exercise stress using standard acquisition protocol of Tl-201 MPI. Similar protocol was used for acquiring redistribution images 3–4 h after the exercise.

Patients were divided into two groups based on the results of the Tl-201 MPI; patients with perfusion defects (MPD, n = 33) and patients with no perfusion defects (no MPD [NMPD], n = 28).

All patients were followed up for 1 year for any cardiac or other health problems. The patients maintained a diary during the follow-up period for the episode of chest pain, breathlessness, palpitations, tightness or heaviness in the chest or any other health problem.

Signal acquisition and processing for HRV

The ECG signals were acquired simultaneously using Nevrokard Multichannel Data Acquisition Software (ADC-8, Slovenia) at sampling rate of 500 Hz for 5 min in supine position after 15 min of supine rest. The acquired signals of ECG were checked for presence of artefacts and corrected following standard protocol. Recordings were discarded if a large number of artefacts were present.

Signal analysis for HRV

The processed ECG signals were analysed using time-domain and frequency-domain methods for HRV measures.[6] Parameters computed in time-domain methods were Standard deviation of the N-N intervals (SDNN), The square root of the mean squared differences of successive N-N intervals (rMSSD), The proportion derived by dividing the number of interval differences of successive N-N intervals greater than 50 ms by the total number of N-N intervals (pNN50) and Coefficient of variance of the R-R intervals (CoV).

In frequency-domain method, spectral powers of different frequency components in HR were analysed using Fast Fourier Transform algorithm. A Hanning window was used and the power spectrum was subsequently plotted for frequency bands very low frequency (VLF) (0.001–0.04 Hz); low frequency (LF) (0.04–0.15 Hz); high frequency (HF) (0.15–0.4 Hz) and for entire band total power (0.001–0.4 Hz). The power was calculated as absolute power in millisecond squares and normalised units (nu). Since VLF value is not appropriate for the short-term analysis of HRV,[6] it was not considered for the present study.

Ejection fraction (EF) and other parameters of patients

EF was calculated from the post-stress gated images in Tl-201 MPI. The left ventricle was also assessed for the regional wall motion abnormalities (if any). The total exercise duration was noted for each patient and the rate pressure product (RPP) was calculated at the maximum exercise during the treadmill stress. The ST segment changes were evaluated from ECG recorded during exercise. Post-stress EF ≥65% was considered normal.

Statistical analysis

The general characteristics among three groups were compared using one-way analysis of variance followed by Bonferroni tests and data are expressed as mean ± SD. The normally distributed HRV parameters were compared using analysis of covariance after adjustment for age, systolic blood pressure (SBP) and HR and are expressed as adjusted mean (95% Confidence Interval). The non-normally distributed HRV parameters were compared using Kruskal–Wallis test followed by multiple comparisons and data are expressed as median (inter-quartile range). $P < 0.05$ was considered statistically significant. The data were analysed using Stata 9.1 (Texas, USA).

RESULTS

Baseline characteristics of MPD, NMPD, and healthy subjects

All patients and healthy subjects were comparable in terms of their height, weight, body mass index, diastolic blood pressure and respiratory rate [Table 1]. Both groups of patients had significantly higher SBP than healthy subjects. The MPD patients had higher age range and NMPD patients had higher HR than healthy subjects. However, all the parameters were comparable between MPD and NMPD patients [Table 1]. Comparison of parameters of HRV among MPD and NMPD patients and healthy subjects was done after adjustment for age, HR and SBP.

The HRV parameters of MPD, NMPD and healthy subjects

The time-domain parameters of HRV (CoV, SDNN, rMSSD and pNN50) and the frequency-domain parameters of HRV (spectral powers of LF, HF and total power) were significantly lower in NMPD patients as compared to both MPD patients and healthy subjects**.** The LFnu and LF/HF ratio was significantly higher and HFnu was significantly lower in NMPD patients than MPD patients, whereas, LFnu, HFnu and LF/HF ratio were comparable between NMPD patients and healthy subjects. All the time-domain and frequency-domain parameters of HRV were comparable between MPD patients and healthy subjects [Table 2].

EF and other parameters of the patients

The MPD patients had significantly lower EF (55.1 ± 12.8 vs. 68.8 ± 2.1, $P = 0.001$) and RPP (22251.3 ± 3153.1 vs. 24828.6 ± 3919.7, $P = 0.006$) than NMPD patients. In 33 MPD patients, 19 (58%) patients had EF <65%, and 23 (70%) patients had regional wall motion abnormalities, whereas in NMPD patients none of the patients had EF <65% and none of the patients had regional wall motion abnormalities. The exercise durations between MPD patients and NMPD patients were comparable (6.38 ± 1.83 vs. 6.49 ± 2.21, $P = 0.839$). In MPD patients, 7 (21%) patients had ST segments depression >2 mm, whereas none of the NMPD patients had ST segments depression or elevation.

Events in MPD and NMPD patients during 1-year follow-up period

Thirty-two patients in MPD group and 25 patients in NMPD group were followed-up for 1 year. One (3.1 %) patient in

Table 1: General characteristics of MPD and NMPD patients and healthy subjects.

Angina patients				MPD versus NMPD patients P_1	MPD versus Healthy subjects P_2	NMPD versus healthy subjects P_3
Parameters	**MPD (*n*=33) (mean±SD)**	**NMPD (*n*=28) (mean±SD)**	**Healthy subjects (*n*=30) (mean±SD)**			
Age (years)	54.9±7.4	53.0±8.5	48.8±6.8	NS	0.010	NS
Height (cm)	167.4±5.6	165.4±6.8	165.6±6.3	NS	NS	NS
Weight (kg)	68.9±8.4	66.9±12.4	66.4±8.2	NS	NS	NS
Body mass index (kg/m^2)	24.6±2.6	24.4±4.0	24.2±2.5	NS	NS	NS
Systolic blood pressure (mmHg)	123.0±12.6	127.1±17.2	113.2±10.6	NS	0.024	0.001
Diastolic blood pressure (mmHg)	79.4±6.4	79.6±8.7	77.2±5.8	NS	NS	NS
Heart rate (bpm)	68.7±10.0	73.7±12.2	64.7±5.6	NS	NS	0.002
Respiratory rate (breath/min)	17.0±2.9	17.3±4.2	17.0±3.8	NS	NS	NS

MPD: Myocardial perfusion defects, NMPD: No myocardial perfusion defects, SD: Standard deviation. $P<0.05$ was considered as statistical significance, NS: No significant difference

Table 2: Comparison of parameters of HRV among MPD and NMPD patients and healthy subjects after adjustment for age, heart rate and systolic blood pressure.

Angina patients				MPD versus NMPD patients P_1	MPD versus healthy subjects P_2	NMPD Versus healthy subjects P_3
Parameters of HRV	**MPD (*n*=33) mean (95% CI)**	**NMPD (*n*=28) mean (95% CI)**	**Healthy subjects (*n*=30) mean (95% CI)**			
Time domain parameters						
CoV (%)	4.4 (4.0–4.8)	3.4 (2.9–3.9)	4.6 (4.2–4.1)	0.001	NS	0.001
SDNN (ms)	39.0 (35.3–42.6)	29.4 (25.3–33.6)	40.0 (36.0–44.1)	0.001	NS	0.001
rMSSD (ms)	30.6 (27.0–34.2)	20.2 (16.1–24.3)	29.3 (25.37–33.3)	0.001	NS	0.004
*pNN50 (%)	3.7 (1.4–9.7)	0.3 (0–1.9)	5.4 (1.4–7.4)	0.001	NS	0.001
Frequency domain parameters						
*LF power (ms^2)	375.1 (262.4–508.8)	158.4 (79.1–296.5)	454.0 (317.7–681.4)	0.006	NS	0.004
*HF power (ms^2)	293.9 (163.7–665.0)	138.0 (77.1–207.4)	287.8 (217.5–594.6)	0.001	NS	0.014
*Total power (ms^2)	1508.0 (748.4–2339.4)	610.1 (379.9–1072.8)	1414.6 (1104.6–2141.5)	0.001	NS	0.001
HF (nu)	46.6 (41.0–52.2)	38.5 (32.2–44.9)	37.8 (31.6–44.0)	0.013	NS	NS
LF (nu)	46.3 (40.7–52.0)	55.3 (48.9–61.8)	53.7 (47.5–60.0)	0.037	NS	NS
*LF/HF ratio	0.9 (0.5–1.4)	1.9 (0.9–2.8)	1.5 (0.9–2.6)	0.015	NS	NS

HRV: Heart rate variability, CoV: Coefficient of variance, SDNN: Standard deviation of the R-R intervals, rMSSD: The square root of the mean squared differences of successive R-R intervals, pNN50: Percentage of the number of interval differences of successive R-R intervals >50 ms divided by total number of R-R intervals, LF: Low frequency, HF: High frequency, nu: normalized unit, MPD: Myocardial perfusion defects, NMPD: No myocardial perfusion defects, ms^2: Millisecond squares, CI: Confidence interval. $P<0.05$ was considered as statistical significance, NS: No significant difference. *Compared using Kruskal–Wallis test followed by multiple comparisons and data are expressed in median (inter-quartile range)

MPD group and 2 (8 %) patients in NMPD group died during the follow-up period (statistically no significant differences). The MPD patient who died was of 62-years-old, had an EF of 58% with fixed perfusion defects in the entire inferior wall extending up to distal inferoapical region, and he suffered from viral fever before the death. The two NMPD patients who died were 40 and 43-years-old, post-stress EFs were 69% and 68%, respectively, RPP was higher in both the patients. Both the patients had no wall motion abnormality, no ST changes, and no signs of neurological or other diseases. No obvious symptoms other than restlessness and nervousness were reported in both the patients before 4–5 h of death. Both patients died after mid night.

DISCUSSION

The study assessed the modulation of cardiac autonomic tone using HRV in patients clinically presenting with angina with MPD and with NMPD and compared them with the HRV of healthy subjects. The major findings of the study were (1) The HRV of MPD patients and healthy subjects were comparable, (2) The NMPD patients had reduced overall

HRV as compared to both MPD patients and healthy subjects and (3) Sudden death within 1 year was seen in both MPD (3.1%) and NMPD (8%) patients.

In the present study, both time-domain and frequency-domain parameters of HRV of MPD patients were comparable to healthy subjects. Similar results were reported in a study by Adamopoulos *et al*.,[21] in which HRV of patients with CAD was comparable to healthy subjects. However, Wennerblom *et al*.[2] reported a reduction in vagal tone in patients with CAD as compared to healthy controls. The differences in results may be due to differences in the study population and other factors. In this study, females and smokers were also included and 24-h Holter recording was performed for HRV, while in the present study only male patients with no other diseases and no history of smoking or alcohol intake were included in the study. Short-term HRV for 5 min was recorded under laboratory conditions. These factors may have affected the results.

In contrast, in the present study, the NMPD patients showed reduced HRV parameters (rMSSD, pNN50 and HF powers) as compared to both MPD patients and healthy subjects. The rMSSD, pNN50 and HF power are considered the markers of parasympathetic tone.[6] Thus, the results revealed the decreased parasympathetic tone in NMPD patients. Similarly, NMPD patients showed reduced other HRV parameters (CoV, SDNN, LF power and total power) as compared to both MPD patients and healthy subjects. These CoV, SDNN and total power are considered the markers of modulation of overall cardiac autonomic tone and the LF power is considered the marker of both sympathetic and parasympathetic tone.[6] Thus, these results revealed decrease in modulation of overall cardiac autonomic tone in NMPD patients.

The HFnu, a marker of parasympathetic tone, was lower in NMPD patients whereas, LFnu and LF/HF ratio, which are markers of sympathetic tone and sympathovagal balance, respectively,[6] was found to be higher in NMPD patients as compared to MPD patients, whereas the NMPD patients and healthy subjects had comparable HFnu, LFnu and LF/HF ratio.

These results revealed that as compared to MPD patients NMPD patients had not only reduced modulation of overall cardiac autonomic tone and parasympathetic tone, but the sympathovagal balance was also shifted towards sympathetic predominance as has been shown in patients after acute MI.[1,7] About 8% of NMPD patients had sudden death during 1-year follow-up in absence of any specific abnormality. Steg *et al*.[22] found about 9.1% of patients clinically presenting with anginal symptoms had no evidence of ischemia. The risk of cardiovascular-related deaths or non-fatal MI occurred greater in those patients than in patients with ischemia alone. It may be due to reduced HRV. The reduced HRV is associated with sudden death.[3] Recently, we reported severe cardiac dysautonomia and sudden death in a patient presenting with anginal symptoms in absence of cardiovascular and other diseases.[17]

The burning question is why these NMPD patients experience angina in absence of myocardial ischaemia and other known systemic diseases and they have risk of sudden death. It may be due to decrease in HRV. Possibly, coronary blood flow and other cardiovascular functions are not adequate to meet the demand of the body during exertion/stress due to reduced modulation of autonomic tone. Thus, lactic acid and other metabolites accumulate in the myocardium, which stimulates cardiac sympathetic afferent fibres that is, nociceptive fibres in the heart and patients develop angina in absence of CAD. In addition to this, stimulation of cardiac afferents reflex tries to enhance sympathetic activation causing increased HR and cardiac contractility. However, modulation of overall cardiac autonomic tone is already reduced in these patients. Thus, possibly it is not compensated appropriately and ultimately cardiac tissues become fatigued and function abnormally towards the ventricular fibrillation and sudden death. The above proposed mechanisms are supported by some experimental studies.

In animal experiments lactic acid and other metabolites, stimulated cardiac sympathetic c-fibre afferents to a greater extent.[23,24] In another study, in sham rats, acute cardiac sympathetic afferent reflex activation by epicardial application of bradykinin increased HR and myocardial contractility.[25]

In human study, Fallen *et al*.[26] studied cardiac energy metabolism in response to stress in three groups of patients with aortic stenosis. (1) Patients with aortic stenosis without angina or CAD showed normal increase in coronary flow, decreased myocardial oxygen extraction and no myocardial lactate production in majority of patients (85%), which suggested that energy supply was adequate to the demand; (2) Patients with aortic stenosis with angina but no CAD showed insignificant increase in coronary flow, increased myocardial oxygen extraction in about 60% of patients and abnormal glycolysis in all patients, which suggested that compensatory mechanisms were not adequate and (3) In aortic stenosis with angina and CAD, coronary flow increased normally, myocardial oxygen extraction decreased normally, but abnormal lactate metabolism occurred in most patients. That suggested adequate overall coronary reserve but evidence of regional ischemia. In case of cardiac ischaemia, sympathetic activation is pro-arrhythmic for ventricular fibrillations leading to sudden death.[27]

Further studies are needed for the exploration of other underlying mechanisms to explain the development of anginal symptoms in patients presenting with angina with NMPD s and other known diseases. It will also help the management of such patients.

CONCLUSION

In the present study, MPD patients showed comparable cardiac autonomic tone to healthy subjects. In contrast, the NMPD patients showed reduced parasympathetic and overall cardiac autonomic tone as compared to both MPD patients and healthy subjects and altered sympathovagal balance in comparison to MPD patients. Surprisingly, sudden death was seen in NMPD patients similar to in MPD patients. A comprehensive study is required to identify the key factors leading to the autonomic neural derangement and sudden death in NMPD group of patients and their management.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Spinnler MT, Lombardi F, Moretti C, Sandrone G, Podio V, Spandonari T, *et al*. Evidence of functional alterations in sympathetic activity after myocardial infarction. Eur Heart J 1993;14:1334-43.
2. Wennerblom B, Lurje L, Solem J, Tygesen H, Udén M, Vahisalo R, *et al*. Reduced heart rate variability in ischemic heart disease is only partially caused by ischemia. An HRV study before and after PTCA. Cardiology 2000;94:146-51.
3. Forslund L, Björkander I, Ericson M, Held C, Kahan T, Rehnqvist N, *et al*. Prognostic implications of autonomic function assessed by analyses of catecholamines and heart rate variability in stable angina pectoris. Heart 2002;87:415-22.
4. Balanescu S, Corlan AD, Dorobantu M, Gherasim L. Prognostic value of heart rate variability after acute myocardial infarction. Med Sci Monit 2004;10:CR307-15.
5. Perkiömäki JS. Heart rate variability and non-linear dynamics in risk stratification. Front Physiol 2011;2:81.
6. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task force of the European society of cardiology and the North American society of pacing and electrophysiology. Eur Heart J 1996;17:354-81.
7. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992;85:164-71.
8. Foreman RD. Mechanism of cardiac pain. Annu Rev Physiol 1999;61:143-67.
9. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, *et al*. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina-summary article: A report of the American college of cardiology/American heart association task force on practice guidelines (committee on the management of patients with chronic stable angina). J Am Coll Cardiol 2003;41:159-68.
10. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, *et al*. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American college of cardiology foundation/American heart association task force on practice guidelines, and the American college of physicians, American association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons. J Am Coll Cardiol 2012;60:2564-603.
11. DePasquale EE, Nody AC, DePuey EG, Garcia EV, Pilcher G, Bredlau C, *et al*. Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease. Circulation 1988;77:316-27.
12. Fintel DJ, Links JM, Brinker JA, Frank TL, Parker M, Becker LC. Improved diagnostic performance of exercise thallium-201 single photon emission computed tomography over planar imaging in the diagnosis of coronary artery disease: A receiver operating characteristic analysis. J Am Coll Cardiol 1989;13:600-12.
13. Matzer L, Kiat H, Van Train K, Germano G, Papanicolaou M, Silagan G, *et al*. Quantitative severity of stress thallium-201 myocardial perfusion single-photon emission computed tomography defects in one-vessel coronary artery disease. Am J Cardiol 1993;72:273-9.
14. Tweddel AC, Martin W, Hutton I. Thallium scans in syndrome X. Br Heart J 1992;68:48-50.
15. Cavusoglu Y, Entok E, Timuralp B, Vardareli E, Kudaiberdieva G, Birdane A, *et al*. Regional distribution and extent of perfusion abnormalities, and the lung to heart uptake ratios during exercise thallium-201 SPECT imaging in patients with cardiac syndrome X. Can J Cardiol 2005;21:57-62.
16. Rosano GM, Ponikowski P, Adamopoulos S, Collins P, Poole-Wilson PA, Coats AJ, *et al*. Abnormal autonomic control of the cardiovascular system in syndrome X. Am J Cardiol 1994;73:1174-9.
17. Khadka R, Narang R, Jaryal AK, Patel C, Deepak KK. Severe cardiac dysautonomia and sudden death in a patient presenting with anginal symptoms in absence of cardiovascular and other diseases: A case report. JNMA J Nepal Med Assoc 2020;58:261-4.
18. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J (Clin Res Ed) 1982;285:916-8.
19. Ritchie JL, Bateman TM, Bonow RO, Crawford MH, Gibbons RJ, Hall RJ, *et al*. Guidelines for clinical use of cardiac radionuclide imaging report of the American college

of cardiology/American 'heart association task force on assessment of diagnostic and therapeutic cardiovascular procedures (committee on radionuclide imaging), developed in collaboration with the American society of nuclear cardiology. J Am Coll Cardiol 1995;25:521-47.
20. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, *et al*. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging executive summary a report of the American college of cardiology/American heart association task force on practice guidelines (ACC/AHA/ASNC committee to revise the 1995 guidelines for the clinical use of cardiac radionuclide imaging). Circulation 2003;108:1404-18.
21. Adamopoulos S, Rosano GM, Ponikowski P, Cerquetani E, Piepoli M, Panagiota F, *et al*. Impaired baroreflex sensitivity and sympathovagal balance in syndrome X. Am J Cardiol 1998;82:862-8.
22. Steg PG, Greenlaw N, Tendera M, Tardif JC, Ferrari R, Al-Zaibag M, *et al*. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: Data from the international observational CLARIFY registry. JAMA Intern Med 2014;174:1651-9.
23. Pan HL, Chen SR. Myocardial ischemia recruits mechanically insensitive cardiac sympathetic afferents in cats. J Neurophysiol 2002;87:660-8.
24. Pan HL, Longhurst JC, Eisenach JC, Chen SR. Role of protons in activation of cardiac sympathetic C fibre afferents during ischaemia in cats. J Physiol 1999;518:857-66.
25. Wang HJ, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent reflex control of cardiac function in normal and chronic heart failure states. J Physiol 2017;595:2519-34.
26. Fallen EL, Elliott WC, Gorlin R. Mechanisms of angina in aortic stenosis. Circulation 1967;36:480-8.
27. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res 2014;114:1004-21.

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