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An Assessment of Autonomic Function Tests in Female Migraine Patients with Aura During Interictal Period.

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ABSTRACT

Migraine is the 3rd most prevalent and 6th leading cause of disability worldwide. It is a chronic neurological disorder that has various autonomic manifestations. Conversely, there are less conclusive studies available regarding dysfunctions of the autonomic functions in female migraineurs during interictal period. To assess and compare the autonomic function tests in female migraine patients during interictal period and age matched healthy female control subjects. Forty diagnosed female migraine patients age ranging between 30-40years, fulfilling the criteria of IHSC-2formed the study group. Age matched 40 healthy female subjects from SMS Medical College were taken as control. For Parasympathetic function tests: 30:15 R-R ratio, Heart rate variation to deep breathing were performed. For Sympathetic function tests: systolic blood pressure change in response to standing, change in diastolic blood pressure with sustained handgrip. Mean 30:15R-R ratio and mean of Heart Rate variation in deep breathing was significantly lower in migraine patients as compared to control subjects(p-value<0.001). Change in systolic blood pressure in response to standing (p-value<0.001) and change in diastolic blood pressure with sustained handgrip was higher in migraine patients (p-value <0.023) during interictal period compared to control subjects. Migraineurs during interictal period are found to have sympathetic hyperactivity and reduced parasympathetic activity. Therefore, an early understanding of the autonomic dysfunctions in migraine patients can help in early diagnosis, prevention and treatment.

Keywords: *Migraineurs with aura, autonomic function, sympathetic hyperactivity*

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INTRODUCTION

The Global Burden of Disease Study 2013found migraine to be the third commonest disease in the world and it is the sixth highest cause of disability worldwide. (1)Migraine is a disabling neurovascular disorder characterized by mostly unilateral throbbing head pain and neurological symptoms including hypersensitivity to light, sound and smell, nausea, and a variety of autonomic, cognitive, emotional and motor disturbances (2,3). The initiation of a migraine attack is frequently associated with a wide variety of internal and external triggers such as stress, hormonal fluctuations, sleep disturbances, skipping meals or sensory overload (4, 5) though, amongst all precipitating factors in migraine, stress being the most common. (6)

There are numerous studies done in the past to suggest that there is an autonomic dysfunction in patients of migraine, sympathetic hyper as well as hypo-functioning and parasympathetic dysfunction have all been noticed.So far, there are less conclusive studies available regarding dysfunctions of the autonomic nervous system in migraineurs during interictal periods.

A better understanding of the autonomic dysfunctions in migraine may help to diagnose, prevent, and/or treat migraine effectively.

MATERIAL AND METHOD

The study was conducted in the Upgraded Department of Physiology in association with the Department of Neurology, S.M.S. Medical college and Hospital, Jaipur, Rajasthan from 1st June 2014 to 31st May 2015.

Forty diagnosed female migraine patients with aura age ranging between 30-40years, fulfilling the criteria of IHSC-2 (International Headache Society Criteria-2*)* formed the study group. Age matched 40 healthy female subjects from SMS Medical College were taken as control subjects.

Ethical Statement:-This study was approved by the Institutional Research Review Board of SMS Medical College and Hospital.

All patients and subjects gave written informed consent to participate in this study categorized into two groups: Group A: female migraine patients with aura; and Group B: healthy female control subjects.

Inclusion criteria: Adult female migraine with aura 30-40 years age**,** follicular phase of regular menstrual cycle (28 days)**,** BMI 18-25 kg/m^2 were included in study.

Exclusion criteria: Body Mass Index ≥ 25 kg/m^2 or ≤18 kg/m^2 **,** Chronic illnesses Diabetes mellitus, Hypertension, Thyroid dysfunction affecting the autonomic function**,** Medications like antihypertensive, antidepressants, anti-anxiety drugs affecting the autonomic functions were excluded from study.

All subjects were tested between 10 am to 12.30 pm under similar laboratory conditions and were allowed to adapt themselves to experimental and environmental conditions for 30 minutes so that they were comfortable, as anxiety and stress can affect autonomic functions. After explaining exact procedure of each test following instructions were given to the subjects

- To avoid coffee, nicotine or alcohol 24 hours prior and food 2 hours prior of autonomic function testing.
- The room ambient temperature was maintained at 24-25°C.

For assessment of Parasympathetic functions following tests were performed:-

- Resting heart rate (beats/ minute)
- Immediate heart rate response to standing (30: 15R-R ratio)
- Heart rate variation during deep breathing (beats/ minute)

For assessment of Sympathetic functions following tests were performed**:-**

- Resting systolic blood pressure and diastolic blood pressure (mm of Hg)
- Change in systolic blood pressure (mm of Hg) in response to standing (after 5 minutes)
- Change in diastolic blood pressure(mm of Hg) in response to sustained handgrip (after 5 minutes)

Immediate heart rate response to standing (30: 15R-R ratio)

The test was performed with the patient lying quietly on a couch. The heart rate was recorded continuously on the ECG machine. The patient was asked to stand up unaided and the point at starting to stand was marked on the ECG. The shortest R-R interval at or around the 15th beat and largest R-R interval at or around the 30th beat after standing was measured.(normal > 1.04, borderline 1.01- 1.03 and abnormal < 1.00).

Heart rate variation during deep breathing

The subject sat quietly and breathed deeply at 6 breaths a minute (5 seconds in, and 5 seconds out) for one minute. An ECG was recorded throughout the period of deep breathing with a mark used to indicate the onset of each inspiration and expiration. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the 6 measured cycles in beats/minute.(normal response >15 beats/minute, borderline 11 - 14 beats/minute and abnormal response < 10 beats/minute).

Change in systolic blood pressure (mm of Hg) in response to standing (after 5 minutes)

The test was performed by measuring the patient's blood pressure with Omron HEM-7120 Automatic blood pressure monitor (digital sphygmomanometer)while subject was lying down quietly and again when she stood up. Blood pressure was measured every minute for 5 minute. The response was taken as the difference between systolic blood pressure after 5 minutes and systolic blood pressure in lying position.(normal response < 10 mm of Hg, borderline 11 - 29 mm of Hg and abnormal response > 30 mm of Hg).

Change in diastolic blood pressure (mm of Hg) in response to sustained handgrip(isometric exercise) (after 5 minutes)

Handgripis maintained at 30% of the maximum voluntary contraction using a handgrip dynamometer for 5 min, and the blood pressure measured each minute with Omron HEM-7120 Automatic blood pressure monitor (digital sphygmomanometer). The difference between the diastolic blood pressure just before release of handgrip, and before starting, is taken as the measure of the response.((normal response > 16 mm of Hg, borderline 11- 15 mm of Hg and abnormal < 10 mm of Hg).

Statistical Analysis

- The numerical data are in the form of mean±SD
- Unpaired student t-test was applied to calculate the level of significance using SPPS version 20.
- Level of significance was assigned at p-value <0.05

RESULTS

The mean of resting heart rate in migraine patients and control subjects was found to be 94.87±6.82 beats/min. and 79.50±4.064 beats/min. respectively.(Table 1)(p- value 0.000))

The mean of Immediate heart rate response to standing (30:15R-R ratio) in migraine patients was found to be 0.988±0.056 as compared to the control group mean 1.108±0.037. (Table 2) (p-value 0.000)

The mean of heart rate variation during deep breathing was found to be10.8±2.18 beats/minfor migraine patients and for the control subjects was found to be18.53±2.11 beats/min. (Table 2) (p-value 0.000)

The mean systolic blood pressure was found to be145.75±8.98 mm of Hg for migraine patients and 122.55±5.06 mm of Hg for control subjects. The diastolic blood pressure was found to be 98.95±7.23 mm of Hgfor migraine patients and for control subjects 78.6±3.45 mm of Hg. (Table 3) (p- value 0.000)

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The mean of change in systolic blood pressure (mm of Hg) in response to standing (after 5 minutes) in migraine patients was found to be 4.35±2.56 mm of Hg and in the control subjects 0.25±1.88 mm of Hg. (Table 3) (p-value 0.000)

The mean of change indiastolic blood pressure response to sustained handgrip in migraine patients was found to be 22.30±3.93 mm of Hg as compared to 20.21±4.12 mm of Hg in the control subjects. (Table 3) (p-value 0.022)

Table 1: Anthropometric parameters

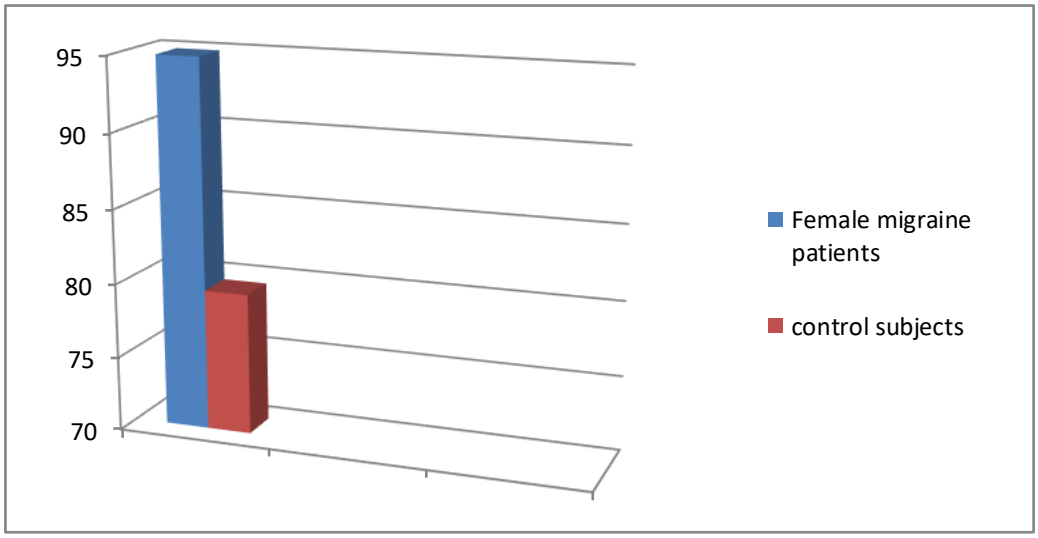
Parameters	Group A -Female migraine patients with aura (n=40)	Group B -Control subjects (n=40)	p- value	Significance
Age (years)	35.15± 3.26	34.20±2.86	0.170	NS
Weight (Kg.)	51.27±3.44	52.52±2.75	0.07	NS
Height (meter)	1.52±0.046	1.53±0.037	0.242	NS
B.M.I.(Kg/m^2)	22.22±1.34	22.42±1.12	0.471	NS

(NS) Non significant, (S) Significant, (HS) Highly significant

Table 2: Parasympathetic function tests

Test parameters	Group A-Female migraine patients with aura (n=40)	Group B-Control subjects (n=40)	p-value	Significance
Resting hear rate (beats/ minute)	94.87±6.82	79.50±4.064	0.001	HS
30-15 R-R ratio	0.988±0.056	1.108±0.037	0.001	HS
Heart rate variation during deep breathing (beats/minute)	10.8± 2.186	18.53±2.11	0.001	HS

(NS) Non significant, (S) Significant, (HS) Highly significant



Histogram 1: showing resting heart rate (beats/min.)

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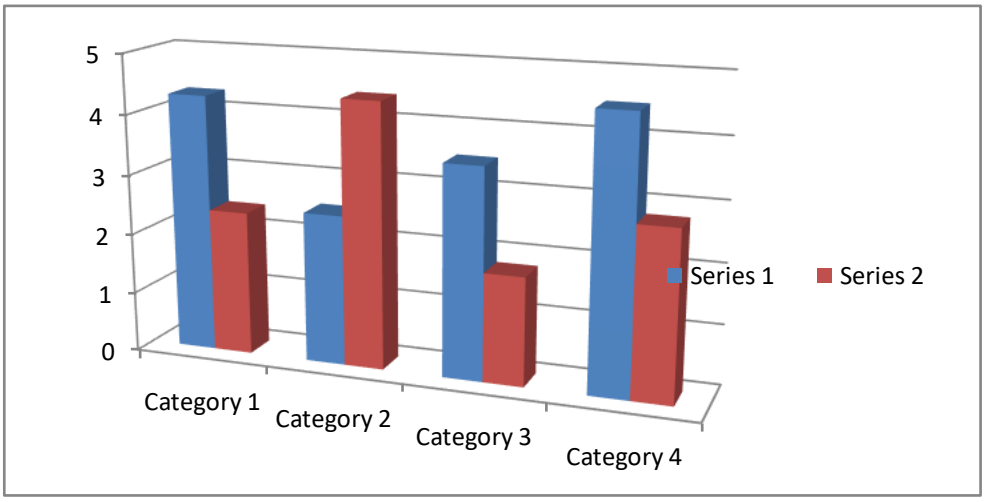
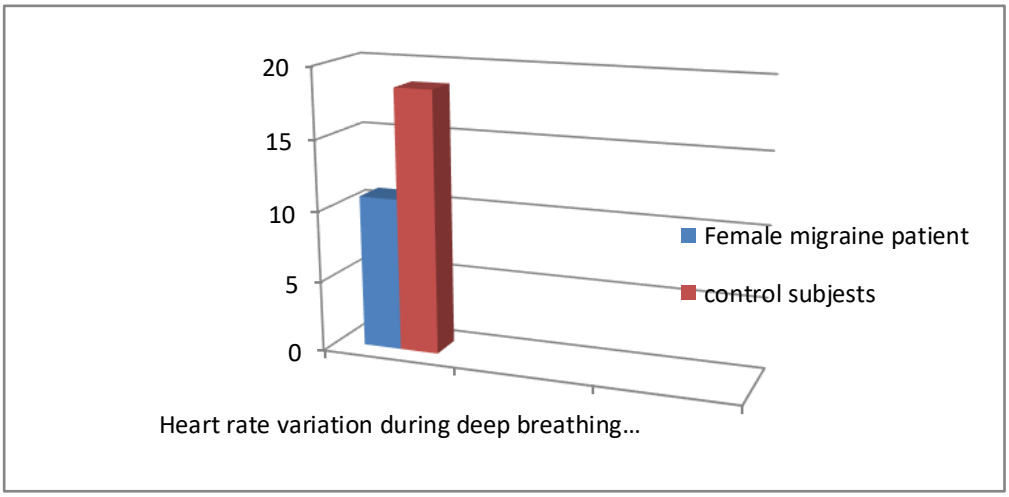


Histogram 2: showing Immediate heart rate response to standing (30 : 15 R-R ratio)



Histogram 3: showing Heart rate variation during deep breathing (beats/minute)

Table 3: Sympathetic function tests

Test parameter	Group A- Female migraine patients with aura (n=40)	Group B-Control subjects (n=40)	p-value	Significance
Resting systolic blood pressure (mm of Hg)	145.75±8.98	122.55±5.06	0.001	HS
Resting diastolic blood pressure (mm of Hg)	98.95±7.23	78.6±3.45	0.001	HS
Change in systolic blood pressure(mm of Hg) in response to standing (after 5min)	4.35±2.56	0.25±1.88	0.001	HS
Change in diastolic blood pressure (mm of Hg) in response to sustained handgrip (after 5 min.)	22.30±3.93	20.21±4.12	0.022	S

(NS) Non significant, (S) Significant, (HS) Highly significant

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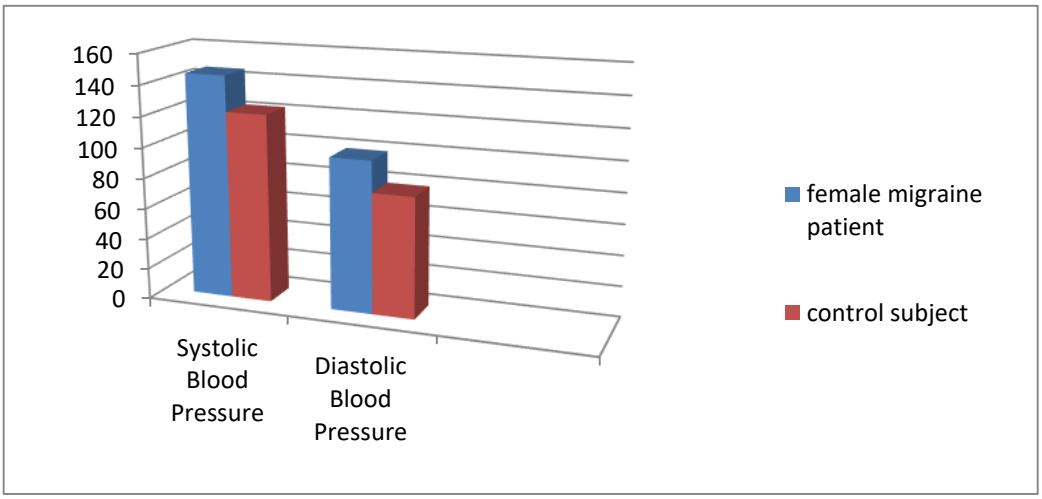
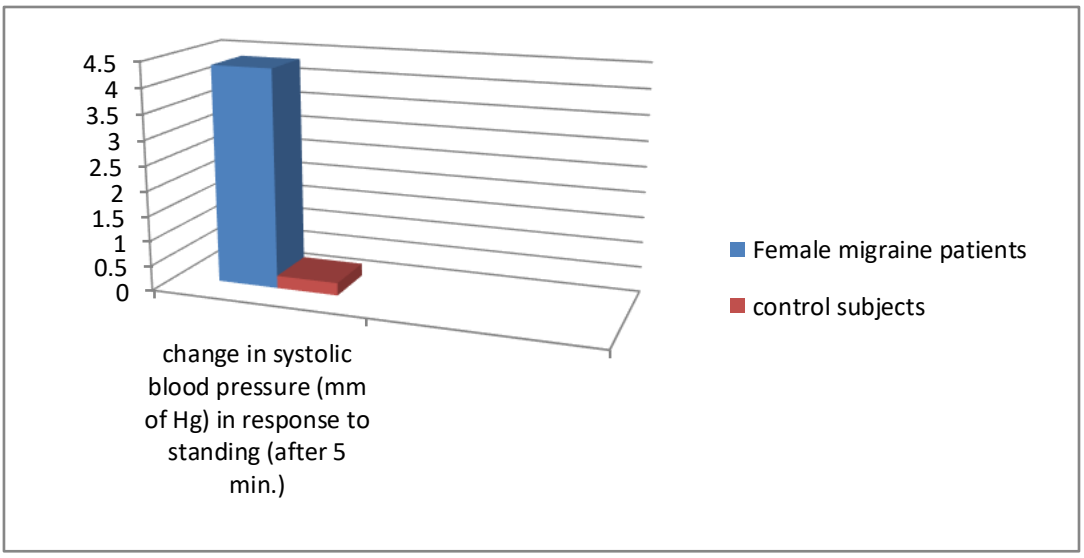
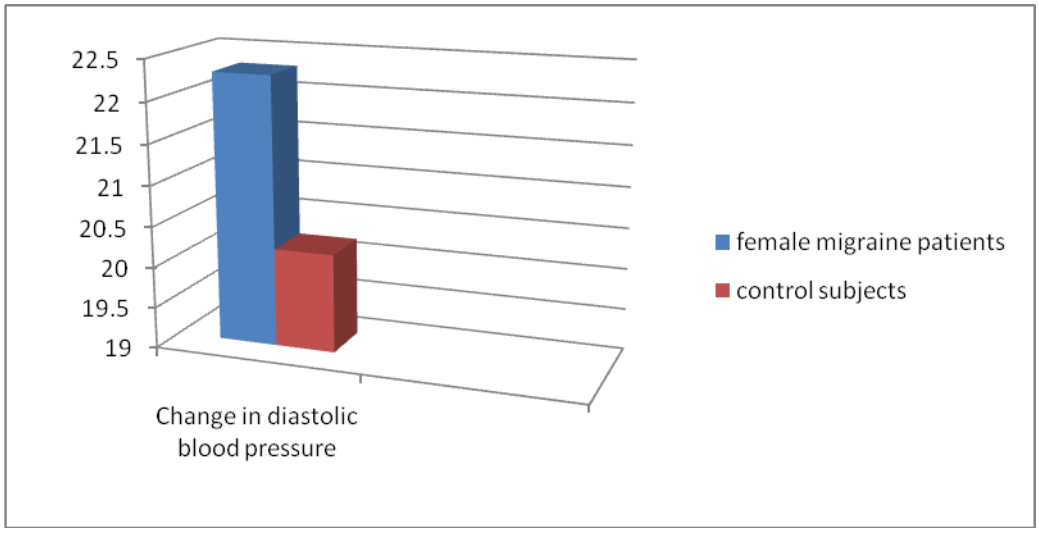


Histogram 4: showing Resting blood pressure in sitting position (mm of Hg)



Histogram 5: showing change in systolic blood pressure (mm of Hg) in response to standing (after 5 minutes)



Histogram 6: showing change in diastolic blood pressure (mm of Hg) in response to sustained handgrip (after 5 minutes)

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DISCUSSION

Cardiovascular autonomic function tests are widely used to detect, corroborate and quantify the cardiovascular autonomic dysfunction. They have been tested for their validity and reliability. Using this background, the present study was undertaken to evaluate the autonomic function tests by using Ewing's cardiovascular reflex tests in female migraine patients and age matched healthy female subjects.

The clinical symptoms of migraine are broadly established to be related to the involvement of the autonomic nervous system and disturbance of the autonomic nervous system, a primary characteristic of migraine. (Melek M. et al) [7]

Based on cardiovascular tests, vasomotor reactions to temperature changes and responses to pharmacological tests, as well as changes in biochemical parameters, hypo- as well as hyper functioning of both the sympathetic and parasympathetic nervous system have been suggested. (Appenzeller O) [8]

A number of case-control studies (Ebinger M.W. et al [9], Appel S. et al [10], Gotoh F. et al [11])of cardiovascular function reported sympathetic hyper function even when using single-lead ECG monitoring in migraine patients in interictal period.

The resting heart rate was found to be more in migraine patients than control subjects. The heart rate is regulated by both the sympathetic and the parasympathetic nervous system, so an increased heart rate in migraine patients could also be interpreted as an increased sympathetic tone or, alternatively, reduced parasympathetic activity. The similar result was also found by Rauschel V et al. [12] and Edahiro S et al. [13] supporting study results.

Normally, the initial heart rate responses to standing consist of a tachycardia followed by a bradycardia. In migraine patients initial tachycardia remain increased due to impaired parasympathetic activity so the 30:15 R-R ratio was lower in migraine patients as compared to control subjects. A similar result was also obtained by Elmenshawy E et al. [14] indicating impaired parasympathetic function in female migraine patients.

Heart rate variation during deep breathing (six-breaths) was significantly reduced in the female migraine patients. This result is concordant with four previous studies of Boiardi A et al. [15], Gotoh F et al. [16], Havanka-Kannianen H et al. [17], Martin R et al. [18] but does not match three clinic-based studies of Cortelli P et al. [19], Cortelli P et al. [20] and Pfeifer MA et al. [21] The other two studies Cortelli P et al. [20] and Pfeifer MA et al. [21] with negative findings had small samples (7 and 13 cases, respectively). RR variation is a measure of variation in heart rate with inspiration and expiration. The absence or a reduction in beat-to-beat variation may indicate an abnormality in sympathetic function or parasympathetic function, a sympathetic stimulation increases heart rate while parasympathetic stimulation decreases heart rate.

We found elevation of systolic blood pressure and diastolic blood pressure among female migraine patients as compared to control subjects in concordance with previous blood pressure studies of Walker CH [22], Launer LJ et al. [23] and D' Alessandro R et al. [24].

As diastolic blood pressure is purely sympathetic function (diameter of blood vessel is maintained by sympathetic system mainly) [25], increased resting diastolic blood pressures here may indicate increased sympathetic tone in migraine patients.

An increased basal sympathetic tone is also suggested by the fact that migraine is associated with more frequent history of hypertension in epidemiological investigations. (Bigal ME et al. [26])

The mean of change in systolic blood pressure (mm of Hg) in response to standing (after 5 minute) in migraine patients was more than in control subjects, a tendency towards increased sympathetic tone as compared to the control subjects.

In sustained hand grip there is sustained muscle contraction which causes a rise in systolic and diastolic blood pressure and heart rate. The stimulus derives from exercising muscle and central command.

Efferent fibers travel to the muscle and heart, resulting in increased cardiac output, blood pressure and heart rate. In migraine patients increase in diastolic blood pressure was more as compared to control subjects. Our study results are in concordant with study conducted by Venkatesan R et al. [27] and Vijayalakshmi I et al. [28], both results showed a trend towards increased sympathetic tone in migraineurs.

Appel et al. [10] used 24-hour EKG Holter recordings to evaluate autonomic functions in migraine patients. By using a spectrum analysis of heart rate fluctuations, he found an increased in power in the lower frequency band (below 0.15 Hz), suggesting sympathetic hyperfunction and a concomitant reduction in the higher frequency band (0.3 Hz) (parasympathetic hypofunction). This may correspond to an imbalance between the sympathetic and parasympathetic function and is consistent with our results.

Exact cause of sympathetic hyperactivity is not proven in migraine patients, possible cause of sympathetic hyperactivity may be stress of headache or imminent headache attack and this is supported by a cross-sectional study, in which migraine patients were found to have elevated plasma levels of cortisol (an indicator for stress) during interictal period in as compared to healthy volunteers (Ziegler DK et al. [29]. It is also supported by stress-provocation study, involving mental stress and physical stressors, which have suggested sympathetic and parasympathetic changes in migraine patients between attacks compared to healthy subjects. Avnon Y et al. [30]

The relation between migraine and autonomic dysfunction is unclear, autonomic dysfunction may be involved in both increased susceptibility to migraine headaches and in response to triggers. Individuals differ in their ability to respond to migraine triggers or precipitants.

A dysfunctional autonomic nervous system might render an individual more susceptible to migraine headache by reacting to triggers at a lower threshold. Circadian and hypothalamic function also may affect autonomic nervous system responses.

In this study, autonomic function tests were performed in morning before11a.m. in all migraine patients and control subjects to minimize the circadian effects.

Migraine patients may suffer from an increased mortality risk due to reduced parasympathetic and increased sympathetic nervous system activity which can lower the threshold for atrial fibrillation, previous studies have reported the association between the autonomic functions and atrial fibrillation. Hohnloser S.H.et al. [31] and P. Coumel [32].

Thus, regular assessment of autonomic functions can be used as a biomarker for early detection and subsequent management of cardiovascular diseases in female migraine patients.

CONCLUSION

The involvement of the autonomic nervous system in migraine pathophysiology is complex and heterogeneous. Most published results suggest either a sympathetic hyperactivity and or parasympathetic hypo-activity. Our study results point in the same direction with a net increased sympathetic tone. Thus, it is concluded that female migraineurs during interictal periods are found to have sympathetic hyperactivity.

Strength, Limitations and Recommendations

- Certainly, the strength of our study is the careful selection and monitoring of the migraine patients, ensuring that all patients were recorded in headache free period and were free of preventive drugs or recent intake of analgesics
- As we only obtained a single interictal recording, it can also not be ruled out that autonomic function test parameters change during the migraine cycle.
- The study was conducted in a limited time period on a small sample size. Better results may be obtained with a larger sample size and larger time period.

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