Asian Journal of Biomedical and Pharmaceutical Sciences
ISSN : 2249 - 622X

RESEARCH ARTICLE

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Received on: 17/06/2014
Accepted on: 30/07/2014
Published on: 15/08/2014

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QR Code for Mobile users

Conflict of Interest: None Declared !

DOI: 10.15272/ajbps.v4i34.516

Assessment of Autonomic Nervous System Status in Severe Iron Deficiency Anemia Patients Using Valsalva Maneuver

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Abstract

Background: The present study was conducted to find out whether the Valsalva test and thus the autonomic nervous system are affected in patients of severe iron deficiency anemia. Materials and methods: In this study the change in heart rate was recorded with the help of ECG machine during and after the valsalva maneuver. The change in heart rate was compared between 60 patients of severe iron deficiency anemia and 60 ages and socioeconomically matched normal subjects. Result: It was found that the change in heart rate was significantly altered in patients of severe iron deficiency anemia ($p<0.0001$) when compared to controls. Conclusion: The present study demonstrates an altered autonomic balance in patients with true iron deficiency anemia.

Keywords: Valsalva test, iron deficiency anemia, heart rate, autonomic nervous system

Cite this article as:
Aniruddha Jibhkate, Sonali Pande. System Status in Severe Iron Deficiency Anemia Patients Using Valsalva Maneuver. Asian Journal of Biomedical and Pharmaceutical Sciences; 04 (34); 2014; 54-58.

INTRODUCTION

Anemia is an independent risk factor for adverse cardiovascular outcomes in the general population[1].The iron status of an individual may play an important role in cardiovascular health, as either an excess of iron or iron deficiency may lead to significant problems[2]. It was previously suggested that anemia was associated with autonomic dysfunctions in ambulatory patients with stable coronary heart disease and that low HRV (Heart rate variation) could potentially mediate the association of anemia with increased cardiac risk[3]. Relation of anemia and autonomic function has been studied in several types of anemia; thalassemia[4], vitamin B_{12} deficiency and megaloblastic anemia[5], sickle cell trait[6].

One third of the world population is suffering from iron deficiency anemia, of which 60% to 70% is in India. The prevalence of iron deficiency anemia is higher among the people living in chronic poverty. Also it tends to run in families, possibly because of economic factors. The iron deficiency anemia is defined by cut off hemoglobin value of 12 gm/dl in women and 13 gm/dl in men. [7]

The autonomic nervous system in our body provides a rapidly responding mechanism to control wide range of functions such as cardiovascular, respiratory, gastrointestinal, renal, endocrine and other systems. All of the above systems are regulated by parasympathetic or sympathetic autonomic nervous systems or both.

Autonomic function is impaired in anemic patients with various etiologies such as vitamin B12 deficiency, sickle cell trait, and thalassemia major. However, there is insufficient data about autonomic functions in patients with iron deficiency anemia, the leading cause for anemia in the general population. In the present study we aimed to investigate the autonomic status in iron deficiency anemia by analyzing the change in heart rate during Valsalva maneuver. Valsalva test is simple, non invasive and reproducible.

MATERIAL AND METHODS

Study population

The study was conducted in Topiwala National medical college and Nair hospital, Mumbai with prior permission of ethical committee. The study was conducted over a period of 2 years.

Inclusion criteria:

Cases

60 patients of severe iron deficiency anemia belonging to the age-group of 20 to 40 years, attending hematology clinic in hospital were selected for study. Patients included were those with:

Severe iron deficiency anemia with [8] All the three conditions when fulfilled by the case then only it was selected for study (cases satisfying all the three conditions were included in the study)

a. Hb level < 7 gm%
b. Serum iron <30 microgram/dl and
c. Total iron binding capacity > 400 micrograms/dl

2) Age group of 20 to 40 yrs.
3) Symptoms of anemia like weakness, early fatigue etc.

Controls

For comparison 60 healthy subjects belonging to age group that is 20 to 40years, same socio-economic conditions were selected from the general population as controls. Having

1) Hb level >12gm% [7]
2) Age group of 20 to 40 yrs.

Exclusion criteria

Subjects of age <20 yrs and>40 yrs.

Subjects with other type of anemia like sickle cell disease, thalassemia, vitamin B12 deficiency were excluded.

Diseases causing autonomic disturbances like diabetes mellitus, Parkinson's disease, multiple sclerosis, asthma, rheumatoid arthritis, hypertension etc. were excluded. [9]

Subjects who were taking medication for iron deficiency anemia like ferrous sulphate etc.

Method

For this study subjects were divided into two groups, that is severe iron deficiency anemia patients and healthy controls. Written consent was taken. Hb level was measured with the help of electronic counter Sysmex k-100. Serum iron and serum total iron binding capacity of the both the groups was measured manually by Ferrozine method.

After this the Resting Heart Rate and Blood Pressure was measured. The heart rate of subject and controls was calculated from ECG tracing and blood pressure was measured in the right upper extremity by sphygmomanometer. The recording was taken only when two consecutive heart rate and blood pressure readings taken 5 minutes apart were identical. This meant that in all probability they had reached their basal values. [10]

After recording the resting heart rate and blood pressure the deep valsalva maneuver test was performed on subjects and patients and alteration in the heart rate was recorded. Procedure was as follows,

Valsalva Maneuver: Heart Rate Response to Valsalva Maneuver

Procedure: To perform the standardized Valsalva maneuver the subject was asked to blow into the tubing of mercury sphygmomanometer and raise the column of mercury to 40 mm Hg. and maintain it at that level for 10 seconds at least i.e. a sustained forced expiratory effort against an obstructed airway. Care

was taken that the pressure rose sharply at onset and fell abruptly at the termination of the strain period. Following a training period each subject performs two Valsalva maneuver separated by a rest period. During each maneuver, heart rate was monitored continuously throughout the strain period and for 15 seconds following release of strain by means of an electrocardiograph. (11)

Mechanism: The phases of Valsalva maneuver were defined by Hamilton:

Phase 1: Rise in blood pressure.

Phase 2: Gradual reduction of blood pressure to plateau, tachycardia.

Phase 3: Fall in blood pressure.

Phase 4: Overshoot of blood pressure, bradycardia.

The increased blood pressure in phase 1 is the result of increased intra –thoracic pressure at the onset of straining. While the rapidly falling blood pressure in phase 2 is caused by reduced venous return producing a fall in cardiac output. In phase 3, release of intra thoracic pressure and consequent rise in pulmonary venous capacitance causes momentary fall in cardiac output occurring at a point where the systemic vascular resistance is still raised in response to baroreflex stimulation produced by the fall in blood pressure in phase 2. (12) The heart rate increases (tachycardia) during the phase when the blood pressure falls. The heart rate decreases (bradycardia) with the overshoot of blood pressure in phase 4.

The heart rate changes during and following the Valsalva maneuver measured by the Valsalva ratio provide a simple and reliable way of assessing the cardiac parasympathetic function in disorders where the autonomic dysfunction is suspected.(10)

Calculations: The heart rate changes induced by the Valsalva maneuver were expressed as the ratio of maximal tachycardia to the maximal bradycardia. This ratio is defined as Valsalva ratio and was calculated as the ratio of the maximal R-R interval to the minimal R-R interval. (10)

Valsalva ratio= Maximal R-R interval (sec) during release/ Minimum R-R interval (sec) during strain

Interpretation of results: the mean of the three Valsalva ratios is taken as the final value. Interpretation of these results is as follows:

Valsalva ratio	
Normal	≥ 1.21
Borderline	1.11-1.20
Abnormal	≤ 1.10

Statistical analysis

Statistical analysis was done by using GraphPadInStat[R] software version 3.10, created on July 10, 2009. Descriptive statistics i.e. mean and standard deviation was used for numerical data. Comparison of numerical variables among groups was done by using unpaired t-test. P – Value< 0.05 was considered as statistically significant.

OBSERVATIONS AND RESULTS

	Group wise comparison of age			Unpaired t- test applied		
	Group	Mean	SD	t-value	p-value	Significance
Age(Yrs)	Cases	25.45	3.92	0.7524	0.4533	Not significant
	Controls	25.85	1.23			

Table No. 1: Comparison of age in cases and controls

In above table, the age of iron deficiency anemia patients (mean 25.45 ± 3.92) is compared with the age of controls (mean 25 ± 1.23) with the help of unpaired t test. From the above results we can conclude that there is no significant difference in the age of both the groups

	GROUP	MEAN	SD	T-VALUE	P-VALUE	SIGNIFICANCE
Heart Rate	Cases	96.5	9.63	8.93	<0.0001	significant.
	Control	82.08	7.94			
Basal systolic blood pressure	Cases	111.50	10.10	4.42	<0.0001	significant.
	Control	118.30	6.30			
Basal diastolic blood pressure	Cases	73.30	8.01	4.28	<0.0001	significant.
	Control	78.56	5.14			
Valsalva ratio	Cases	1.19	0.025	2.433	0.0165	Significant.

Table No. 2: Group wise comparison of various parameters

The above table shows the values of meanand standard deviation of various parameters like heart rate, systolic blood pressure, diastolic blood pressure, and heart rate variation during deep breathing test.

The mean heart rate of patients (96.5 ±9.63) was found to be significantly (<0.0001) higher thanthat of controls (82.08± 7.94).

The mean systolic blood pressure of patients (111.50 ± 10.10) was found to be significantly (<0.0001) lower than that of controls (118.30 ± 6.30).

The mean diastolic blood pressure of patients (73.30 ± 8.01) was significantly (<0.0001) lower than that of controls (78.56 ± 5.14).

The mean heart rate variation during valsalva maneuver test in patients was found to 1.19 ± 0.025 and it was 1.27 ± 0.05 in controls.. It was found that the heart rate variation during deep breathing test was significantly (<0.0001) lower in cases than that of controls.

DISCUSSION

Iron deficiency is the most common nutritional deficiency in developed and developing regions of the world. The physiologic response to anemia is a compensatory increase in cardiac output through increases in blood volume, preload, heart rate, and stroke volume, along with a decrease in afterload. Therefore, the increased sympathetic activity, evidenced as palpitation and tachycardia, is frequent in patients with anemia[13]. An extreme result of iron deficiency is cardiomyopathy. The pathogenesis of cardiomyopathy associated with anemia has not been ascertained. Several hypotheses have been advanced to explain how iron-deficiency anemia causes cardiomyopathy. It has been suggested that, similarly to other types of heart failure, high-output heart failure is driven by ongoing increased sympathetic nervous activity[2].

The aim of the present study was to find out whether the Valsalva maneuver test and thus the autonomic activity affected in iron deficiency anemia patients or not.

Both the study group (patients of iron deficiency anemia and controls) were matched for age. This is very important because there are previous studies which suggest that advancing age is known to diminish the vagal tone,[14] which affects the autonomic functions.

Resting heart rate: In present study, a comparison between the resting heart rate in iron deficiency anemia patients and controls was made. The basal heart rate in iron deficiency anemia patients was 96.5 ± 9.63 and in controls it was 82.08 ± 7.94. Thus there was increase in heart rate in iron deficiency anemia patients which was statistically significant(<0.0001) as compared to control subjects.

Findings of this study correlate with those of NityaNand et al who also found higher basal heart rate in severely anemic patients (p <0.001) in their study of autonomic functions in chronic severe anemic patients.[15]Lakhotia et al in their study Clinical assessment of autonomic functions in anemics noted increase in heart rate of anemics. According to their study short circulatory time and peripheral vasodilatation occurred as a compensatory mechanism to increase the heart rate in anemics. [16]

Glick et al in the year, 1964 also found increased heart rate in acutely induced anemia in unanesthetised dogs. He suggested that this increased heart rate could be due to 1) elevation of right atrial pressure, which, by increasing the tension of the atrial wall may increase the rhythmicity of the sinoatrial node, 2) local metabolic changes resulting from the changes in tissue partial pressure of oxygen produced by anemia and 3) noncatecholamine humoral substances released during anemia. [17] In humans, lack of oxygenation in tissue due to anemia results in local accumulation of metabolite like lactic acid due to anaerobic metabolism. This leads to vasodilatation and consequent increase in heart rate.[18]. In present studythe decreased peripheral resistance may be the cause for increased heart rate in iron deficiency anemia patients.

Resting blood pressure: The mean systolic blood pressure in iron deficiency anemia patients was 111.50 ± 10.10 and in controls it was 118.30 ± 6.30. Thus the systolic blood pressure is significantly lower (<0.0001) in iron deficiency anemia patients. Also the mean diastolic blood pressure in iron deficiency anemia patients was 73.30 ± 8.01 and in controls it was 78.56 ± 5.84. This means diastolic blood pressure was also significantly (<0.0001) lower in iron deficiency anemia patients.

Nitya Nand et al in their study on chronic severe anemic patients found low systolic as well as diastolic blood pressure (P<0.001). [15] Justus et al in their study on chronic post hemorrhagic anemia in dogs, found that in response to infusion of blood at the rate of 1.0/ml/kg/min there was decrease in both cardiac output and arterial tension. [18]

The blood pressure is lateral force exerted by the flowing blood against any unit area of vessel wall. [19] In iron deficiency anemia to fulfill the oxygen demand of tissue due to decrease oxygen content of blood, there occurs increase in cardiac output. Although the mechanism responsible for this increase in cardiac output has not been elucidated, a number of possibilities have been suggested. These include a decrease in peripheral resistance resulting from a fall in blood viscosity and arteriolar dilatation, an elevation of right heart filling pressures, stimulation of chemoreceptors sensitive to a decreased partial pressure of oxygen, the action of a non catecholamine humoral mediator, and the activity of the adrenergic nervous system. [18]

The blood pressure is maintained by the cardiac output and the total peripheral resistance and these two show significant inverse relationship, that is, higher the cardiac output the lower is the vascular resistance. [20] The mechanism for decreased peripheral resistance in anemia is controversial. Justus et al in their study suggested that increased cardiac output and decreased peripheral resistance was due to humoral agents. However the exact nature and the mechanism of action of the agents are not specified. According to them several possible humoral agents which decrease peripheral vascular resistance include adrenal medullary hormones, V.E.M., serotonin and others. [18] Whereas Glick et al postulated a neural mechanism for decrease peripheral vascular resistance. According to this study, anemia profoundly reduces the tissue

oxygen tension. Such a reduction in tissue oxygen tension, lowers the total systemic resistance through local effects. [17] Local fall in oxygen tension initiates a program of vasodilatory gene expression secondary to production of Hypoxia inducible factor- 1α, thus causing arteriolar dilation resulting in secondary increase in cardiac output. [21]

Thus the results of present study showed a significant fall in both systolic and diastolic blood pressure in anemics as compared to controls and this fall in blood pressure may be the result of decreased peripheral resistance due to anemia. [20]

Heart rate variation during Valsalva maneuver: The heart rate response to Valsalva maneuver in severe iron deficiency anemia patients was found to be 1.19 ± 0.025 and it was 1.27 ± 0.05 in controls. Significantly low values for heart rate response to Valsalva maneuver in severe iron deficiency anemia patients was found when compared to controls.

Valsalva maneuver elicit complex scale of hemodynamic events that results in the activation of sympathetic and parasympathetic neurons. It has been suggested that the cardiac response to Valsalva maneuver should be represented by the increase or decrease in heart rate relative to the initial heart rate. Both these indices correlate closely with the Valsalva ratio. Thus, the Valsalva maneuver is reflection of both sympathetic and parasympathetic activity. (14)

Nitya Nand et al in their study on patients with chronic severe anemia reported abnormal Valsalva ratio. They suggested that this finding implicates dysfunction of afferent limbs of the parasympathetic. (15) However Lakhotia et al in their study found that the test requiring stimulation of parasympathetic system that is Valsalva manoeuvre did not show any significant difference in anemics and control. (19)

In the present study 40% of the iron deficiency anemia patient had abnormal Valsalva ratio, thereby suggesting autonomic dysfunction insevere iron deficiency anemia patients.

CONCLUSION

Thus, from the results of present study,it can be concluded that there occurs autonomic dysfunction in severe iron deficiency anemia patients. The autonomic reflex arc can be tested valsalva maneuver, which is reliable, simple, non invasive. The autonomic nervous system controls wide range of functions such as cardiovascular, respiratory, gastrointestinal, renal, endocrine and other systems. Therefore it is necessary to further study autonomic dysfunctions occurring in iron deficiency anemia patients.

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