Research Article

# A study of autonomic functions in patients with iron deficiency anaemia

Brinda Venkatraman[1*], Prasad A Udhoji[2], Yogesh G Patle[3]

[1]Professor and HOD, [2]Assistant Professor, Department of Physiology, Topiwala National Medical College and BYL Nair Ch. Hospital, Mumbai-400008, Maharashtra, INDIA.
[3]Assistant Professor, Department of Pathology, Peoples College of Medical Sciences and Research Centre, Bhopal-462037, Madhya Pradesh, INDIA.
**Email:** brindav56@gmail.com, dr.prasadudhoji@gmail.com, drygpatle1983@gmail.com

## Abstract

**Background and Objectives:** Iron deficiency anaemia (IDA) is possibly a most common nutritional disorder having widespread occurrence throughout the world. Anaemia has been associated with various cardiovascular outcomes such as left ventricular dysfunction, cardiomyopathy etc. along with increasing morbidity and mortality. Since most of the physiological alterations occuring in chronic anaemic states are cardiovascular in nature and autonomic nervous system (ANS) has a major role to play in all cardiovascular adjustments, intactness of normal functioning of ANS is of importance. Our objective was to study the integrity of ANS in chronic IDA using standard tests for autonomic functions, to compare autonomic functions in IDA patients with normal controls, and to infer whether IDA of more than 6 months duration with Hb levels of less than 10 gm% shows any dysfunction in autonomic machinery and to explore the possible causes of dysfunction. **Methods**: 30 anaemic patients with Hb < 10 gm% and 30 normal controls were included in study. Their hemoglobin levels were determined and standard tests to determine autonomic functions (Resting HR and BP, Expiration – Inspiration ratio, Postural tachycardia index, Valsalva ratio, sustained hand grip and cold pressor tests,) were carried out in them. **Results:** Statistical evaluation was done using unpaired 't' test. Except for Resting HR and Expiration – Inspiration ratio, other autonomic function tests showed statistically significant difference between the patients and controls ($p<0.05$) **Interpretation and Conclusion:** Chronic anaemia impairs the integrity of ANS and the blunted baroreceptor and chemoreceptor response may be responsible for its causation.
**Keywords:** Autonomic function tests, Baroreceptors, Chemoreceptors, IDA.

[*]**Address for Correspondence:**
Dr. Prasad A Udhoji, 206-B wing, Garden Tower, Lokhandwala township, Akurli road, Kandivali East, Mumbai-400101, Maharashtra, INDIA.
**Email:** dr.prasadudhoji@gmail.com
Received Date: 28/05/2015 Revised Date: 08/06/2015 Accepted Date: 10/05/2015

| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.statperson.com |
| | DOI: 11 June 2015 |

## INTRODUCTION

Iron deficiency anaemia (IDA) is probably the most common nutritional disorder in the world. Anemia is an independent risk factor for adverse cardiovascular outcomes increasing overall morbidity and mortality[1-3]. The incidence of Iron deficiency anaemia is high in developing countries like India due to multiple factors like poverty, malnutrition, poor environmental sanitation, parasitic infestations, diarrheal episodes etc. Most of the physiologic alterations occuring in chronic anaemia (such as peripheral vasodilation, redistribution of blood flow, increased cardiac output) are cardiovascular in nature. Autonomic nervous system (ANS) has a major role to play in all cardiovascular adjustments, whether it is long term or transient[4-7]. Autonomic function is impaired in anaemic patients with various etiologies such as vitamin B12 deficiency, sickle cell trait, and thalassemia major. However, recently less studies are being carried out relating ANS with IDA, and there are insufficient data about autonomic functions in patients with iron deficiency anaemia, which is the leading cause of anaemia globally[8]. Therefore, we attempted this study to find out whether autonomic nervous system shows altered functions under the influence of physiologic changes in

How to site this article: Brinda Venkatraman, Prasad A Udhoji, Yogesh G Patle. A study of autonomic functions in patients with iron deficiency anaemia. *International Journal of Recent Trends in Science and Technology* June 2015; 15(2): 313-317 http://www.statperson.com (accessed 12 June 2015).

patients with chronic Iron deficiency anaemia. It is also important to determine the status of the autonomic machinery in order to preconceive how the body is likely to react to certain drug regimes, to determine the stressful effect of surgery or to learn about other complications which may occur.

## MATERIALS AND METHODS

The study was undertaken after acquiring the institutional ethics committee approval. The study was conducted in 60 subjects who were divided into 2 groups, study group and control. The purpose of the study and brief explanation of the tests to be performed were given to them before procuring a signed consent of their willingness to comply. The first group consisted of 30 IDA patients in the age group of 20-40 years. Of these, 18 were males and 12 were females. All had Hb levels of less than 10 gm% with varied symptoms of anaemia of more than 6 months but had no previous history of any treatment taken for anaemia. The second group consisted of 30 controls in the age group of 20-40 years with a Hb of more than 12 gm% in females and 13 gm% in males. This group consisted of 17 males and 13 females.

Exclusion criteria for patients and controls:

- Subjects taking any treatment for IDA
- Subjects having any addictions to alcohol, tobacco, drugs etc
- Diseases causing autonomic disturbances like diabetes mellitus, parkinson's disease, multiple sclerosis, asthma, rheumatoid arthritis, hypertension, chronic lung diseases, hepatic dysfunction[9].

Hemoglobin levels of both groups were tested in an electronic cell counter (Coulter D.T.). Both groups were then subjected to series of tests performed within the college laboratory while exercising utmost care in the conduction so as to achieve the maximum possible accuracy in the set up. The parameters used to study autonomic nervous system are[10-15]

1. Resting heart rate(RHR) and blood pressure (BP)
2. Heart rate response to deep breathing (Sinus arrhythmia)
3. Heart rate response to standing (Postural tachycardia index)
4. Heart rate response to valsalva manouevre (Valsalva ratio)
5. Blood pressure response to cold-pressor test
6. Blood pressure response to sustained hand grip

### Resting heart rate and blood pressure

Each subject was made to lie down on a couch and after a rest of 5 minutes, the resting pulse and blood pressure (BP) was recorded in the lying posture. Heart rate was calculated from ECG tracing taken on a portable machine 'Cardiomin'. BP was recorded in right upper extremity with a mercury sphygmomanometer. Subsequently 2 more readings were taken at 5 minutes intervals and the test was started after 2 consecutive readings were the same.

### Heart rate response to deep breathing

This is sinus arrhythmia. While the subject was lying supine, he was asked to breathe slowly and deeply at the rate of 6 breaths per minute, with each phase of respiration i.e. inspiration and expiration lasting for 5 seconds each. A metronome was used to adjust the timing. After a few seconds of practice, a continuous ECG tracing was taken. On the recorded ECG tracing, Expiration-Inspiration index (E/I ratio) was calculated as follows:

Expiration – Inspiration index = Maximum R-R interval in mm during Expiration / minimum R-R interval during Inspiration

### Heart rate response to standing

This is Postural tachycardia index (PT index), which may be defined as the beat to beat variability recorded during the immediate heat rate response to standing from a supine position. Only the limb leads of the ECG were attached to the subject and the subject was instructed to stand up with his feet on a mat placed beside the couch, causing the least possible movement in order to avoid motion artifacts. A continuous ECG tracing was taken from the time the subject started getting up to a few seconds after standing still. Postural index was calculated from the ECG tracing in the following way: Postural index = Maximum R-R interval at $30^{th}$ beat / Minimum R-R interval at $15^{th}$ beat

### Heart rate response to valsalva manoeuvre

To perform the valsalva manoeuvre, subject was made to sit on a stool and blow into the rubber tube of a mercury sphygmomanometer to raise the mercury column to 40 mmHg and to maintain that level for at least 30 seconds. A continuous ECG tracing was recorded during the whole manoeuvre. Valsalva index was calculated as follows:

Valsalva index = Maximum R-R interval in mm during release / Maximum R-R interval in mm during strain

### Cold pressor test

The subject was to keep his left hand dipped in ice cold water at 4ºC for at least one minute. Blood pressure was measured simultaneously in the other hand. The difference in systolic and diastolic pressures before and during the test was recorded for each subject.

### Sustained hand grip test

A sphygmomanometer cuff was rolled over and partially inflated upto 20 mmHg. Subject was asked to use maximum voluntary effort of contraction (MVC) for the first measurement by asking him to press the cuff maximally by his left hand. The level to which the

mercury column rise was noted. Then he was instructed to maintain the hand grip steadily at 30% of MVC for as long as possible. BP was recorded in the right arm as the left arm was exercised. The difference in systolic and diastolic pressure before and during the test was recorded for each subject. All the above tests are specifically selected because their validity and reproducibility were confirmed as tests for autonomic functions.

## OBSERVATIONS AND RESULTS

An evaluation of autonomic functions in 30 IDA patients was done in comparison with autonomic functions in 30 healthy controls of comparable age and sex. The mean age of the patients was 28 years and that of the controls was 29.5 years. The mean hemoglobin of the patients was 6.4 gm% and that of controls was 13.8 gm %. The results of this study were based on statistical evaluation using unpaired 't' test. Resting heart rate – did not show any significant difference in anaemic patients. ( $p > 0.05$) (Table no.1) Resting blood pressure – both systolic and diastolic blood pressures did show a significant difference in both the systolic and diastolic blood pressures in anaemic patients showing significant lower values ( $p < 0.01$) (Table no.1)

**Table 1:** Resting values of heart rate and blood pressure

| | Mean ± S.D. (controls) | Mean ± S.D. (patients) | Level of significance |
|---|---|---|---|
| Resting heart rate (RHR) | 75.8 ± 7.1 | 76.36 ± 11.2 | P > 0.05 |
| Systolic blood pressure (SBP) | 117 ± 12.3 | 106 ± 6.3 | P< 0.05 |
| Diastolic blood pressure (DBP) | 73.7 ± 8.5 | 66 ± 6.7 | P <0.05 |

Expiration – Inspiration index did not show statistically significant difference between the two groups ($p > 0.05$) (Table no.2) Postural tachycardia index was found to be abnormal in atleast 12 % cases and there was a significant difference in the 30:15 beat R-R interval ratios between IDA patients and normal controls ( $p < 0.01$) signifying abnormal vagal function. (Table no.2) Valsalva ratio was also significant ($p < 0.001$) and 60 % cases showed abnormal response. (Table no.2)

**Table 2:** Heart rate variation

| | Mean ± S.D. (controls) | Mean ± S.D. (patients) | Level of significance |
|---|---|---|---|
| Expiration – Inspiration ratio | 1.25 ± 0.5 | 1.28 ± 0.5 | P>0.05 |
| Postural tachycardia index | 1.3 ± 0.15 | 1.15 ± 0.2 | P<0.05 |
| Valsalva ratio | 1.37 ± 0.13 | 1.12 ± 0.2 | P<0.05 |

Cold pressor test showed a positively abnormal response in 40 % of cases with a diastolic rise of less than 10 mmHg ($p < 0.05$) (Table no.3) Response to sustained hand grip in anaemic patients was also significant ($p < 0.05$) when compared to normal controls. (Table no.3)

**Table 3:** Blood pressure variation

| | | Mean ± S.D. (controls) | Mean ± S.D. (patients) | Level of significance |
|---|---|---|---|---|
| Cold pressor test | SBP | 13.8 ± 5 | 7.3 ± 2.5 | P<0.05 |
| | DBP | 12.1 ± 6 | 8.1 ± 2.5 | P<0.05 |
| Hand grip test | SBP | 14.6 ± 5.5 | 7.3 ± 5.8 | P<0.05 |
| | DBP | 12.8 ± 5.4 | 7.1 ± 4.7 | P<0.05 |

## DISCUSSION

Iron deficiency anaemia is defined by cut-off Hb value of 12 g/dl in women and 13 g/dl in men. Iron deficiency anaemia occurs as a late manifestation of prolonged negative iron balance. Human body has 3-4 g of iron out of which 60-70% is in Hb and any Iron deficiency anaemia in this will therefore cause iron deficiency anaemia[16]. Multiple etiological factors are involved in iron deficiency anaemia.

- Decreased intake of iron in diet
- Impaired absorption of iron
- Increased iron loss due to hemorrhage
- Increased physiological need for iron
- Inadequate presentation to erythroid precursors
- Abnormal iron balance

Vasomotor changes in iron deficiency anaemia occur due to involvement of ANS[17]. Autonomic function tests were performed after matching both the groups (patients and control) for age. This is important because studies suggest that autonomic functions become impaired with advancing age. K.J.Collins stated that the decline in efficiency of homeostatic regulation with age is due to diminishing competence of ANS[18]. The following reference values of Ewing and Clark were used to interpret the results of the Autonomic function tests[19]:

| Sr. No | Autonomic Function Tests | Normal | Borderline | Abnormal |
|---|---|---|---|---|
| 1 | HR variation to deep breathing | ≥ 15/min | 11-14 | ≤10 |
| 2 | Decrease in SBP on standing | ≤ 10 mmHg | 11-29 | ≥ 30 |
| 3 | 30:15 ratio | ≥1.04 | 1.01 – 1.03 | ≤ 1.00 |
| 4 | Valsalva ratio | ≥ 1.21 | 1.11 – 1.20 | ≤ 1.0 |
| 5 | Increase in DBP to cold pressor test | ≥ 11 mmHg | - | ≤ 10 |
| 6 | Increase in DBP to sustained hand grip | ≥ 16 mmHg | 11-15 | ≤ 10 |

In this study, at least 21 patients had one abnormal response but this response could not be correlated to either the duration or severity of anaemia. The baroreceptor and chemoreceptor functions which may be blunted by the effect of chronic system hypoxaemia, largely influence autonomic functions. Abnormal response elicited during the tests could thus be attributed primarily to abnormal receptor sensitivity.

The part of the reflex arc tested by autonomic function tests are as follows [20]:

1. Heart rate variability with respiration – vagal afferent + efferent limbs
2. Heart rate response to standing - vagal afferent + efferent limbs
3. Valsalva ratio - vagal afferent + efferent limbs
4. BP response to standing - vagal afferent + Sympathetic efferent
5. Isometric exercise(Hand Grip test) – sympathetic efferent
6. Cold pressor test - sympathetic efferent

The most important test for autonomic integrity is the valsalva manouevre. Valsalva index is a reflection of both sympathetic and parasympathetic activities. Altered valsalva ratio encountered in this study suggests an abnormality in parasympathetic reflex arc. Parasympathetic dysfunction is manifested by the failure of the heart to slow during phase IV of BP overshoot. However, the cold-pressor response was also found to be abnormal suggesting some abnormality in the sympathetic arc as well. Values for Hand grip test which also assesses the integrity of the sympathetic reflex arc, was found to be significant in this study. It is more likely to be a false positive result, since the test is effort dependent and BP response could vary depending on a varied /lower MVC (maximum voluntary contraction) rather than efferent sympathetic activity. Since heart rate variation during standing is under vagal control, the Postural Tachycardia index (PT index) offers rebound bradycardia (R-R interval) at the 30$^{th}$ beat as parameter for assessing integrity of vagal function. An abnormal PT index could probably explain postural hypotension and other related symptoms in anaemia. However this study could not record any difference of statistical significance in the E/I ratio probably because more than one afferent input are involved – peripheral baroreceptors, chemoreceptors and cardio-pulmonary stretch receptors. The duration of one deep inspiration being only 5 seconds and therefore probably not sufficient to elicit an abnormal response unless the abnormality is acutely manifest. It could also be because of inability of the patient to conform to the given instructions.

## CONCLUSION

It may be concluded that in all likelihood, the parasympathetic reflex arc is affected. However, it cannot be affirmed on the basis of these tests that which aspect of the reflex arc is affected. Since the cold pressor response was also abnormal, the sympathetic reflex arc was also found to be affected, inspite of the assumption that adrenergic impulses to capacitance vessels are already at a high in anaemic states. Expiration / Inspiration ratio was not positively abnormal but its findings were supportive of abnormal parasympathetic functions. Hand grip test can be considered inconclusive because of the inbility of the patients to maintain the required MVC levels. Thus it may be concluded that blunting of baroreceptors and chemoreceptors due to chronic hypoxia may be the root-cause of dysfunction of parasympathetic reflex arc in chronic IDA. It was not possible to pinpoint the exact site of the lesion in the parasympathetic reflex arc or the sympathetic reflex arc since that would require some more specific tests for functions of afferent and efferent pathways.

## REFERENCES


1. Sarnak MJ, Levey AS, Schoolwerth AC *et al*. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and epidemiology and Prevention. Circulation. 2003;108:2154-69,
2. Sarnak MJ, Tighiouart H, Manjunath G *et al*. Anemia as a risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol. 2002;40:27-33,
3. Hakki S, Yilmaz G, Sengiz D et l. The effects of iron deficiency anaemia on p wave duration and dispersion. Clinics 2010; 65 (11): 1067-71.
4. De Gruchi: Clinical hematology in medical practice. 5$^{th}$ edition.1990; 25-27.
5. Elwood PC: Evaluation of clinical importance of

anaemia. Am.J Clin.Nutrition. 1973; 26(9):958-964.
6. Roy S B, Bhatia M L, Mathia V S *et al*: Haemodynamic effects of chronic severe anaemia. Circulation.1963; 28:346-357.
7. Varat MA, Adolph RJ, Fowler NO: Cardiovascular effects of anaemia. Am. Heart J.1972; 83 (3):415-426.
8. Yokusoglu M, Nevruz O, Baysan O *et al*. The altered autonomic nervous system activity in Iron deficiency anaemia. Tohoku J.Exp.Med., 2007; 212:397-402.
9. Goldstein DS, Robertson D, Esler M *et al*., Dysautonomias: Clinical disorders of the ANS. Ann.Intern.Med.2002; 137(9): 753-763.
10. Deepak KK *et al*: Autonomic dysfunction and peipheral vasodilatory response in diabetics. Indian J. of Physiol. And Pharmacol. 1996; 40 (4): 326-329.
11. Khanam AA *et al*: Study of pulmonary and autonomic functions of asthma patients after yoga training. Indian J. of Physiol.And Pharmacol. 1996; 40 (4): 314-324.
12. Moriarty K T *et al*: Cardiovascular autonomic function tests. J .Neurol. Neurosurg. and Psychiatry. 1991; 54 (10): 938-959.
13. Pate D, Thomsen *et al*: clinical assessment of autonomic nervous system. Anaesthesiology. 1968; 29: 623.
14. William L, Henrish: Autonomic insufficiency. Archives of internal medicine. 1982; 142: 339-344.
15. Nanaiah A, Chowdhury SD, Jeyaraman K, *et al*., Prevalence of cardiac autonomic neuropathy inj Asian Indian patients with fibrocalculus pancreatic diabetes. Indian journal of endocrinology and metabolism, sept-oct 2012; 16 (5):749-753.
16. Park K. Text book of preventive and social medicine 2011; 21st edition, 575-576.
17. Adamko D.J., Agarwal N, Alter B.P *et al*. Wintrobes clinical hematology 12th edition 2009: 810-830.
18. Bannister Roger: Autonomic failure: A text book of clinical disorders of the ANS, Oxford univ press, 1983; 496-545.
19. Ewing DJ, Clark BF. Diagnosis and management of diabetic autonomic neuropathy; British Medical Journal 1982; 285(2): 916-918.
20. Raymond D.Adams. Principle of Neurology; 7th edition 2001: 550-563.

Source of Support: None Declared
Conflict of Interest: None Declared