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Critical Evaluation of Fear As Aetiological factor for Development of Heart Disease In Albino Rats WSR To Electrocardiography

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Abstract

During the past three decades the number of deaths due to CVDs has increased from 15.2% to 28.1% in India. There are many dietary and lifestyle factors are responsible for this rise. In the common aetiology of heart diseases stated by Acharya Charaka, along with other causes, psychological causes like *Chinta* (worry), *Bhaya* (Fear/Anxiety), *Manasik Trass* (mental tension) are mentioned as factors responsible for heart disease. There is sharp increase in cases of anxiety and depression due to change lifestyle in present era. Hence, it is essential to evaluate the role of *Ayurvedokta* psychological factor such as *Bhaya* (Anxiety) in the development of heart disease. Chronic unpredictable mild stress (CUMS) is the most elegant model for evaluation of anxiety in the rats as this model possesses construct, predictive and face validity in rats. Hence, this model is used in the present study. In CUMS process, animals will be subjected chronically and unpredictably to a variety of **low-grade stressors** which resembles to those associated with anxiety like symptoms in humans and also cause cognition impairment. It is observed that CUMS had generated the anxiety in rats leading to alteration in normal cardiac physiology. ECG is the commonest diagnostic tool which is used to diagnose cardiac abnormalities in both humans and animals. In present study, ECG was done using ketamine anaesthesia and all measurements are decided accordingly. After confirmation of stress in animals, Electrocardiography parameters are checked using Data Acquisition System, Powerlab. Significant changes were observed in disease control group indicating that fear lead to cardiac discomfort in experimental rats.

Keywords : *Chinta* , *Bhaya* ,*Manasik Trass*, ECG

Introduction :

Nearly there are 3 million (30 lac) cases of Myocardial Infarction occurs every year (API Study) in India and 15 million (1.5 Cr.) cases across the globe every year. Out of this, 25% are under 40 age, 50% are under 50 age, 25% > 50 years of age. The death due to myocardial infarction is increasing in Indian population at an alarming rate and accounts for around 15-20% of all deaths. During the past three decades the number of deaths due to CVDs has increased from 15.2% to 28.1% in India. [1] The number of factors play role in the development of ischemic heart diseases but over consumption of oily fatty food and unhealthy lifestyle (*mithya ahar vihar*) with mental stress are the important basic factors enumerated by both the science. In Ayurveda it can be called as '*Hrit Aposhanaj Hrit Roga*' and the pathophysiology of MI is mentioned by Sushruta in Sutrasthana 15/32 and Syndrome of MI is mentioned by Sushrut Uttartantra 43/131-132 in the form of '*Hrit Shoola*'. In the common aetiology of heart diseases stated by acharya Charaka, along with other causes, psychological causes like *Chinta* (worry), *Bhaya* (Fear/Anxiety), *manasik trass* (mental tension) are mentioned as factors responsible for heart disease. [2,3]

There is sharp increase in cases of anxiety and depression due to change lifestyle in present era. Hence, it is essential to evaluate the role of Ayurvedokta psychological factor such as *Bhaya* (Fear/Anxiety) in the development of heart disease. Stress is an important factor having high impact on the psychological development which alters emotion, cognition and related behavioral outputs.

The Chronic Unpredictable Mild Stress (CUMS)

model in rats is a widely used animal model for inducing depressive-like behaviors by exposing rodents to a series of random, mild stressors over several weeks. This model is designed to mimic the cumulative effects of daily life stressors that contribute to anxiety and depression in humans. CUMS leads to disruption of homeostasis, causing somatic, physiological, neurobiological, biochemical, and behavioral disturbances. [4] ECG is the most popular method of knowing the heart rhythm and ischemic abnormalities. In rats, ECG is recorded with or without giving the anaesthesia to the rats. **Telemetry** is the method which records the ECG without giving the anaesthesia. in present study, ECG was done using ketamine anaesthesia and all measurements are decided accordingly. After confirmation of stress in animals, Electrocardiography parameters are checked using Data Acquisition System, Power lab.

Review Of Literature :

Chronic unpredictable mild stress (CUMS) is the most elegant model for evaluation of anxiety as this model possesses construct, predictive and face validity in rats. In CUMS process, animals will be subjected chronically and unpredictably to a variety of **low-grade stressors** which resembles to those associated with anxiety like symptoms in humans and also cause cognition impairment. CUMS protocol is performed in separate room but the normal animal left unchallenged. During the 7 weeks, animals were submitted to 6 different stressors: tilted cage (45°), food and water deprivation, restricted access to food, exposure to empty bottle, 24 h wet cage (200ml of water in 100g of sawdust bedding), continuous illumination.

These stressors are randomly scheduled over a week period and are repeated to maintain the aspect of unpredictability. At the end of every week sucrose consumption test and body weight of all animal are measured to confirm the induction of stress in animals. [5]

There are several invasive and non invasive techniques to record 1 to 12 channel ECG recordings in rats. Most studies use limb lead II which is sufficient for general analysis of ECG parameters in rats. Surface ECG recordings is the most commonly used technique in anesthetized rats. To obtain a limb lead ECG, the electrodes are placed under the skin of left and right forepaws and the tail. In this technique, measurements may be confounded by type of anaesthesia. Telemetry is the method which records the ECG without giving the anaesthesia. Telemetry transmitters are implanted subcutaneously in the abdominal cavity or intrascapular region whereas electrodes connected to the transmitters are placed the anterior mediastinum. Data from transmitters are gathered wirelessly by a receiver placed outside the rat cage. This method provides data that is free of anaesthesia. [6] However, in present study, ECG was done using ketamine anaesthesia and all measurements are decided accordingly. After confirmation of stress in animals, Electrocardiography parameters are checked using Data Acquisition System, Power lab.

Myocardial Infarction (MI) :

MI refers to the condition where there is imbalance between the myocardial oxygen demand and its supply due to the obstruction of blood supply in coronary arteries. [7] [8]

The commonest causes responsible for it are :

- Atherosclerosis in coronary artery
- Thrombosis

Investigations To Diagnose MI :

- **Lipid profile** – It may show dyslipidaemia (Increased LDL cholesterol and Triglycerides)
- **Cardiac Markers** - Serum Troponin and CPK-MB elevated.
- **ECG** shows ST-T changes. In rats ST segment is absent in waveforms.
- **Coronary Angiography (CAG)** shows coronary occlusions.
- **2-D Echocardiography** shows regional wall motion abnormalities. [20 & 21]

Research Question :

Whether Ayurvedokta *Bhaya* (fear) acts as a aetiological factor for development of heart disease.

Hypothesis :

- **Null Hypothesis (H1):**
Ayurvedokta *Bhaya* (fear) factor acts as a aetiological factor for development of heart disease
- **Alternate Hypothesis (H0):**
Ayurvedokta *Bhaya* (fear) factor does not acts as an aetiological factor for development of heart disease.

Aims & Objectives :

- **Primary Objectives:**
The present study, aims to study the aetiological factor *Bhaya* (**Fear/Anxiety**) as the cause for the development of heart disease.

• **Other Objectives:**

To study the aetiopathogenesis of myocardial infarction from Ayurvedic point of view.

1. Tilted cage (45°),
2. Tail clamping for 3 minutes,
3. Cold swimming for 5 minutes at 4°C
4. Exposure to empty bottle,
5. 24 h wet cage,
6. Continuous illumination.

Material & Methodology :

Study Design :

Center of Study – Dept of Roga Nidana & Vikrutvigyana, Government Ayurvedic College, Nanded And National Testing Centre, Pune

Duration of Study – 18 months

Study Population And Sampling

Animal required for the Study

Species/Common name - Albino Rat

Weight - 200-250 g

Gender – Male and Female

Number to be used - 12

Groups :

Animals will be divided into 2 groups.

Groups (n = 6)	Treatment
Normal Control	No treatment
Disease Control	Chronic unpredictable mild stress induction

Data Collection & Instruments :

The animals will be subjected chronically and unpredictably to a variety of **low-grade stressors** which resembles to those associated with anxiety like symptoms in humans and also cause cognition impairment. CUMS protocol will be performed in separate room. During the 7 weeks, animals will be submitted to 6 different stressors:

These stressors will be randomly scheduled over a one week period and will be repeated to maintain the aspect of unpredictability. After confirmation of stress in animals, ECG was done using the power Lab data acquisition apparatus on 0, 28th and 49th Day. Rats were anaesthetized with Ketamine before taking the ECG.

Assessment Criteria:

1. ECG is monitored in 8 Channel power laboratory (Data Acquisition system) and different ECG parameters are measured.

RR interval is the time between the two consecutive R wave peaks. In rats Heart rate is calculated using RR interval only because rat ECG lacks the Q waves. (HR = 60/ (R-R interval in seconds). In matured rats RR interval is 118-251ms.

PR interval is measured from the beginning of the P wave to the beginning of the QRS/RS complex. The PR interval in rats ranges from 38 to 70 ms. It is significantly affected by the type of anaesthesia used. It is 56 to 66 ms in rats anaesthetized with Ketamine.

QRS complex is located between Q and S wave. It represents the time taken by wave of depolarization to move through the ventricles. Narrowing of QRS is seen in supraventricular arrhythmias whereas widening of QRS is seen in Ventricular arrhythmia and bundle branch blocks. Since Q wave is not

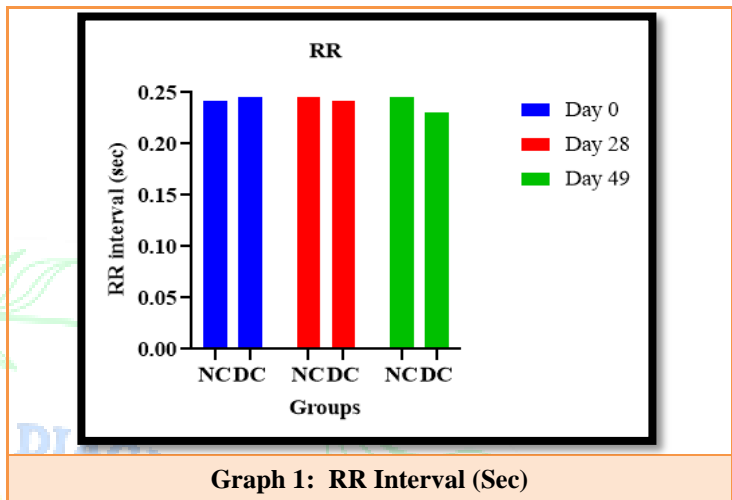
usually detectable in Rat ECG, usually the RS complexes are evaluated. The duration of QRS in rats under ether anesthesia is 11.3to 16.1 ms. And 12 to 15.7 in rats anaesthetized with Ketamine.

QT interval is the time taken from the Q wave to the end of the T wave. In rats this parameter is usually measured from the onset of Rs complex to the end of T wave. QT interval represents the time of depolarization and repolarization of ventricles. It may be affected due to intrinsic heart diseases or drug toxicity. A prolonged QT interval in rats also been found in hypokalemia and myocardial infarction. QT interval in rats is also affected by the type of anaesthesia used. In SD rats it is 50-70ms. Whereas in rats anesthetized with ketamin, it is found to be 75-95ms. In rats anesthetized with ether, it is found to be 60.6- 62.5 ms.

Observation & Result :

Table No. 1 – RR Interval (Sec) :

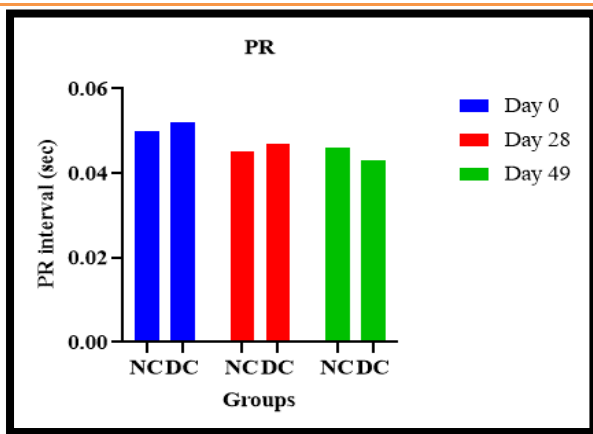
Days		Day 0	Day 28	Day 49
Group	Ani. No	RR	RR	RR
NC	1	0.222	0.217	0.225
	2	0.254	0.257	0.252
	3	0.233	0.239	0.235
	4	0.259	0.254	0.265
	5	0.237	0.248	0.246
	6	0.249	0.251	0.255
	Mean	0.242	0.244	0.246
	SD	0.014	0.015	0.014
DC	7	0.251	0.253	0.258
	8	0.235	0.232	0.228
	9	0.234	0.230	0.218
	10	0.248	0.247	0.221
	11	0.252	0.243	0.231
	12	0.250	0.249	0.232
	Mean	0.245	0.242	0.231
	SD	0.008	0.009	0.014



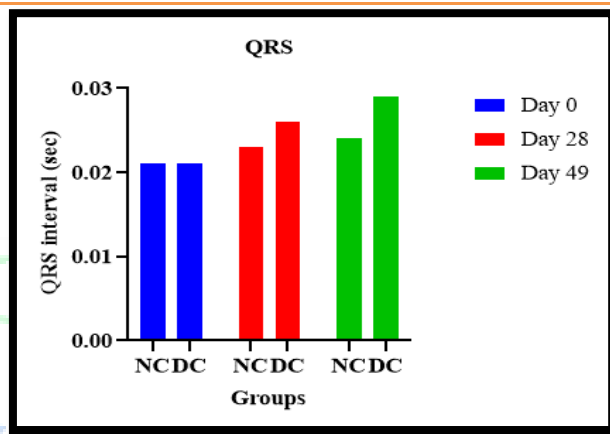
Graph 1: RR Interval (Sec)

Table No. 2 – PR Interval (Sec) :

Days		Day 0	Day 28	Day 49
Group	Ani. No	PR	PR	PR
NC	1	0.049	0.050	0.059
	2	0.052	0.053	0.022
	3	0.048	0.051	0.048
	4	0.050	0.050	0.045
	5	0.049	0.013	0.051
	6	0.050	0.054	0.052
	Mean	0.050	0.045	0.046
	SD	0.001	0.016	0.013
DC	7	0.056	0.044	0.040
	8	0.055	0.052	0.047
	9	0.056	0.046	0.039
	10	0.051	0.050	0.048
	11	0.045	0.043	0.042
	12	0.049	0.048	0.042
	Mean	0.052	0.047	0.043
	SD	0.004	0.004	0.004



Graph 2: PR Interval (Sec)



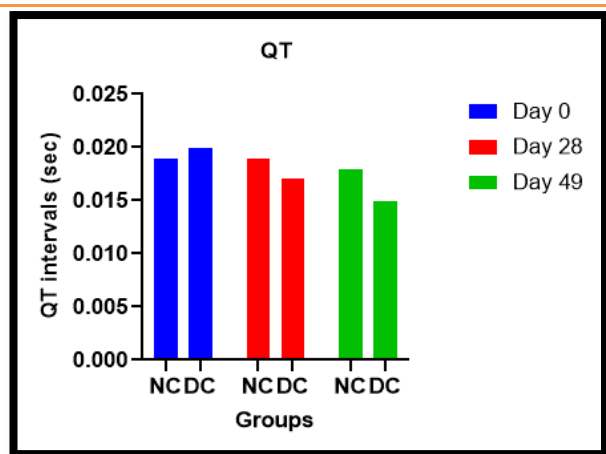
Graph 3: QRS (Sec) :

Table No. 3 – QRS (Sec) :

Days		Day 0	Day 28	Day 49
Group	Ani. No	QRS	QRS	QRS
NC	1	0.026	0.019	0.015
	2	0.014	0.029	0.035
	3	0.026	0.007	0.024
	4	0.025	0.023	0.022
	5	0.016	0.023	0.036
	6	0.020	0.038	0.014
	Mean	0.021	0.023	0.024
	SD	0.005	0.010	0.009
DC	7	0.023	0.022	0.025
	8	0.022	0.023	0.026
	9	0.012	0.023	0.023
	10	0.025	0.026	0.027
	11	0.023	0.028	0.032
	12	0.020	0.032	0.039
	Mean	0.021	0.026	0.029
	SD	0.005	0.004	0.006

Table No. 4 – QT Interval (Sec) :

Days		Day 0	Day 28	Day 49
Group	Ani. No	QT	QT	QT
NC	1	0.021	0.021	0.021
	2	0.016	0.018	0.020
	3	0.016	0.018	0.016
	4	0.025	0.022	0.018
	5	0.020	0.016	0.019
	6	0.016	0.018	0.015
	Mean	0.019	0.019	0.018
	SD	0.004	0.002	0.002
DC	7	0.021	0.015	0.014
	8	0.021	0.016	0.015
	9	0.021	0.018	0.016
	10	0.020	0.018	0.012
	11	0.014	0.017	0.013
	12	0.020	0.020	0.018
	Mean	0.020	0.017	0.015
	SD	0.003	0.002	0.002



Graph 4: QT Interval (Sec)

Discussion :

Long-term exposure to stressful conditions is associated with the development of a manifold of pathophysiological conditions, including those affecting behaviour, immune physiology, neuronal signalling, and cardiovascular function as well as chronic mood disorders such as anxiety and depression. (Glaser & Kiecolt-Glaser, 2005) [9]

This requires animal models to validate the casualty between stress and overt development of heart disease. Chronic unpredictable mild stress (CUMS) is the most elegant model for evaluation of anxiety as this model possesses construct, predictive and face validity in rats. Accordingly, this model was used in present study. [10] Animals were subjected to 6 different stressors: tilted cage (45°), food and water deprivation, restricted access to food, exposure to empty bottle, 24 h wet cage (200ml of water in 100g of sawdust bedding), continuous illumination. These stressors will be randomly scheduled over a week period and are repeated to maintain the aspect of unpredictability.

As per researches, CUMS model leads to many behavioral changes and changes in brain structure

and function, including alterations in neurotransmitter systems (e.g., serotonin, dopamine, and norepinephrine), neurotrophic factors, and stress hormone levels. The unpredictable nature of the stressors more closely resembles the chronic, unpredictable stressors experienced in real human life. ECG is the most popular method of knowing the heart rhythm and ischemic abnormalities.

In rats, ECG is recorded with or without giving the anaesthesia to the rats. In present study, ECG was done using ketamine anaesthesia and all measurements are decided accordingly.

The mean RR interval observed in normal control on day 0 is **0.242** whereas in Disease control, it is **0.245**. The mean RR interval observed in normal control on day 14 is **0.244** whereas in Disease control, it is **0.242**.

The mean RR interval observed in normal control on day 42 is **0.246** whereas in Disease control, it is **0.231**. RR interval found to be decreased on day 28 in DC which was not statistically significant. While on Day 49 statistically significant decrease was seen in DC as compared to NC indicating the effect of stressors on RR Interval.

The mean PR interval observed in normal control on day 0 is **0.050** whereas in Disease control, it is **0.052**.

The mean PR interval observed in normal control on day 14 is **0.045** whereas in Disease control, it is **0.047**. The mean PR interval observed in normal control on day 42 is **0.046** whereas in Disease control, it is **0.043**. On all the three measurements there is rise in blood pressure in disease control

indicating that stress had increased the blood pressure. The mean QRS observed in normal control on day 0 is **0.021** whereas in Disease

control, it is **0.021**. The mean QRS observed in normal control on day 14 is **0.023** whereas in Disease control, it is **0.026**. The mean QRS observed in normal control on day 42 is **0.024** whereas in Disease control, it is **0.029**.

No significant change in the PR & QRS interval is observed.

The mean QT interval observed in normal control on day 0 is **0.019** whereas in Disease control, it is **0.020**.

The mean QT interval observed in normal control on day 14 is **0.018** whereas in Disease control, it is **0.017**. The mean QT interval observed in normal control on day 42 is **0.018** whereas in Disease control, it is **0.015**.

QT interval has decreased on day 28 but not statistically significant.

Summary & Conclusion :

1. RR interval found to be decreased on day 28 in DC which was not statistically significant. While on Day 49 statistically significant decrease was seen in DC as compared to NC indicating the effect of stressors on RR Interval.
2. PR- No significant change in the PR & QRS interval. These results indicate no change in stress.
3. QT interval has decreased on day 28 but not statistically significant.
4. On the basis of the ECG parameters like RR interval and QT interval results obtained, it can be concluded that *Bhaya* fear can acts as an etiological factor for the development of heart disease in rats.

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