

HEART RATE VARIABILITY IN HYPERTHYROID PATIENTS

CORRELATED WITH THYROID FUNCTION TESTS

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INTRODUCTION

The thyroid is a highly vascular, brownish-red structure located in the neck anteriorly extending from fifth cervical vertebra to the first thoracic vertebra ¹.

Thyroid gland is the largest gland which is essential to sustain normal life .

Thyroid is a greek word meaning "shield", introduced by Thomas Wharton².

Thyroid gland consists of follicles lined by cuboidal epithelium. Each follicle contains clear proteinaceous colloid material. The colloid consists of mainly thyroglobulin. Iodide plays a important role in thyroid synthesis. About 120 µg of iodide enter thyroid gland per day. The iodide pump or Na⁺/I⁻ (sodium iodide symporter) reabsorbs iodide into thyrocytes against electrical gradient. Iodine is immediately bound to the tyrosine in the thyroglobulin³.

Thyroglobulin is iodinated to form monoiodothyrosine(MIT) and diiodothyrosine (DIT). By coupling reactions, thyroxine(tetraiodothyronine) T₄, triiodothyronine T₃ and reverse T₃ are formed. Thyroid peroxidase helps in both iodination and coupling reactions .

At the peripheral tissues, triiodothyronine is produced from the deiodination of thyroxine . T₃ has shorter half life but more active than T₄.

When the thyroid gland become overactive and synthesize excess of thyroid hormone ,it is called hyperthyroidism. The prevalence of hyperthyroidism has been estimated as 0.21 percent for men and 1.9 percent for women ⁴.

The most common cause of hyperthyroidism in younger age group is Graves' disease .

In graves the total daily disposal of T_3 is disproportionately increased relative to that of T_4 , indicating that the production rate of T_3 is increased . it could be due to increase in thyroid secretion of Triiodothyronine .Deiodinase -1 also causes increased peripheral conversion of T_4 to T_3 .

Temporary viremia of thyroid gland, certain drugs, toxic nodules can also cause hyperthyroidism .

Thyroid stimulating immunoglobulins are the antibodies that activate the TSH-receptor, thereby stimulating thyroid hormone synthesis and results in diffusely enlarged goiter . This is the etiology for graves disease.

In most patients thyroid gland is massively enlarged or of normal size in a small fraction of patients.The consistency varies from soft to firm and rubbery. The surface may be lobular or smooth. Continous thrills and bruits at the upper or lower thyroid pole, due to increased blood flow ,which is suggestive of hyperthyroidism due to graves disease ⁵ .

Major emotional Stress and fright before a year or so can be a cause for the autoimmune activity in Graves' disease patients⁶.

It is unusually seen in men. In females, it is more prevalent after puberty. The reason for this difference being gonadal steroids and estrogen. These hormones attack the B lymphocyte population. But androgens may suppress autoimmune activity in most of the men, so Graves incidence in men is less.

In female patients with hyperthyroidism, pregnancy and delivery are precipitating events for Graves' disease⁷.

In patients with Graves disease, the thyroid gland is characterised by a non homogenous infiltration with an absence of follicular destruction. The degree of infiltration can be reduced by proper antithyroid treatment⁸.

Although the intrathyroidal lymphocyte population is mixed, most are T- lymphocytes. B cell germinal centres are less common than in autoimmune thyroiditis.

Symptoms:

Symptoms of Graves' disease include goiter, nervousness, bruit over the thyroid, problems in conceiving, increased sleeping pulse rate, palpitations, dry and brittle hair, oligomenorrhea and amenorrhea, loss of weight, increased

perspiration, warm moist skin, lid retraction, frequent bowel movements, thinning of hair, hand tremors, heat insensitivity and pretibial myxedema⁹.

Tachycardia is almost always present, and tachycardia during sleep pulse rate >90 beats per minute distinguish tachycardia of thyrotoxic origin from that of psychogenic causes¹⁰.

Graves' ophthalmopathy presents with symptoms that include dry, gritty ocular sensation, photophobia, double vision and pressure sensation behind the eye.

Increase in connective tissue is due to the hydrophilic ground substance accumulation like hyaluronic acid and chondritin sulphate.

Digital swelling, clubbing, and sub periosteal reaction of toes and fingers is called Thyroid Acropachy.

Dermopathy is seen in 99% of graves ophthalmopathy with increased content of hyaluronic acid and chondritin sulphate and lymphokine activated fibroblasts.

Thyroid dermopathy is most commonly manifested on the legs as pretibial myxedema¹¹. TSH receptor expression is seen in the fibroblasts and adipocytes.

Autoimmune thyroid diseases are due to antigen specificity in suppressor and regulatory T lymphocyte function.¹²

This disease is rare before ten years of age. Hashimoto's disease and Graves' disease are autoimmune disorder and females are mostly affected in both. There are many reasons for developing Graves' disease . Genetic predisposition or family history may play a leading role in thyroid disorders. Stress can be one of the environmental factors for thyroid autoimmunity¹³.

Thyroid storm is also called thyrotoxic crisis usually occur in association with graves disease . It is a sudden incident when the thyroid hormones reach toxic levels with fever, perspiration, tachycardia and hypertension. The clinical picture is severe with hypermetabolism , accompanied by congestive heart failure, pulmonary edema. Incidence of thyroid storm is about 10% in hospital admissions precipitated by trauma, surgical emergencies, infections . It is ten times more common in females. It has a mortality rate of 20 to 30%¹⁴.

Other causes for hyperthyroidism are,

Toxic Multinodular Goiter:

Few nodular and spherical growths are seen in the thyroid lobes. These nodules cause increased synthesis of thyroxine and triiodothyronines¹⁵.

Seen in patients over 50 yrs of age. Nodules become overactive after many years of thyroid enlargement.

Somatic mutations in the TSH receptor gene demonstrated in toxic adenomas in some cases of toxic multinodular goitre and appeared to be different from nodule to nodule.

Overmedication with Thyroid Hormone:

Levothyroxine given for hypothyroidism due to disease, radioactive iodine, can cause hyperthyroidism.

Excessive Iodine Ingestion:

High iodine content in cough syrup and amiodarone, an antiarrhythmic drug can cause hyperthyroidism in certain patients. Amiodarone reduce the effects of hyperthyroidism. The clinical diagnosis of amiodarone induced hyperthyroidism is difficult. Iodine may destroy thyrocytes and release thyroid agglutinogens to the body's immune system.

Postpartum Thyroiditis:

Pregnancy is a state of immunosuppression due to increased steroid hormone levels. When pregnancy proceeds from first to last trimester, the disease ameliorates and after delivery the autoimmune processes flare up and may lead to the emergence of post partum thyroiditis¹⁶.

Thyroid stimulating antibody declines in the third trimester of pregnancy but passively transferred to foetus¹⁷. In few cases mild to moderate postpartum hyperthyroidism is seen. Hyperthyroidism lasts for 1 to 2 months followed by several months of hypothyroidism. Most women will recover. In few cases hypothyroidism needs thyroid hormone replacement.

Subacute Thyroiditis:

It may follow a viral infection with painful thyroid gland. It is a self-limited condition associated with hyperthyroidism, hypothyroidism, and finally euthyroidism. Subacute thyroiditis accounts for 15-20% of thyrotoxicosis patients¹⁸.

Silent Thyroiditis:

Silent thyroiditis is thyroid gland inflammation, in which the person alternates between hyperthyroidism and hypothyroidism. Symptoms similar to postpartum

thyroiditis. It has both painful and painless variants and sometimes biopsy of the thyroid gland reveals the histopathological changes of Hashimoto's thyroiditis³².

Irradiation:

In the general population whom were previously exposed to radiation, thyroid auto antibodies are common. Transient clinical ophthalmopathy can occur due to radioactive iodine.

Infection:

Y. enterocolitica and other infections of the thyroid gland like congenital rubella can be the etiology for hyperthyroidism and commonly associated with thyroid autoimmune phenomena¹⁹.

TSH, T₃ and T₄ Regulation:

Anterior pituitary gland produce thyroid-stimulating hormone (TSH), which regulates thyroxine and triiodothyronine synthesis from thyroid gland. TSH has been shown to be secreted in a pulsatile manner in adults²⁰.

TSH production itself is regulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus .

TSH synthesised by anterior pituitary is regulated by negative feedback mechanism. The TSH receptor is G –protein linked with seven trans membrane domains and employs cyclic adenosine monophosphate and phosphoinositol pathways for signal transduction .

When the $T_3 T_4$ levels are high , they act on anterior pituitary and rapidly suppress TSH production. Low levels of thyroid hormones stimulate pituitary TSH Secretion and increase $T_3 T_4$ synthesis from the thyroid gland.

On exposure to cold, hypothalamus via TRH, increase TSH secretion from anterior pituitary and during warmth, reduce TSH secretion.

Emotional conditions like anxiety, excitement, fear arouse the sympathetic nervous system and decrease TSH secretion. Both temperature modulations and emotional effects were not observed, after the transection of hypophysial stalk, since both these effects were mediated by the way of hypothalamus²¹.

TSH is essential for increasing the number of thyrocytes, proteolysis of thyroglobulin, iodide pumping, iodination of tyrosine and for synthetic functions of thyrocytes.

Too little iodide, or too much iodide decreases iodide trapping and also thyroid hormone synthesis. Sodium –iodide symporter,(NIS) needs TSH for its positioning on plasma membrane. NIS loses its ability to transport iodide across the plasma membrane in the absence of TSH .

TSH production is decreased by growth hormone inhibiting hormone , rising levels of steroids secreted from adrenal cortex . Binding of Thyroid stimulating hormone to its receptor on the thyrocytes increases cAMP levels. Cyclic AMP activates protein kinase which phosphorylates the cell and causes the growth of thyroid glandular tissue and increase thyroid hormone secretion ²².

Cardiovascular and extra cardiovascular manifestations of hyperthyroidism are due to hyperadrenergic state ²³.

Thyroid hormones is vital for stimulating metabolic processes and it increases the demand for coenzymes and vitamins. Basal metabolic rate is increased by increasing the number of mitochondria and also by increasing the activity of sodium potassium ATPase pump.

One consequence of this activity is to increase body heat production and oxygen consumption and ATP hydrolysis rate. Thus body temperature parallels thyroid hormone fluctuations.

Hyperthyroid patients usually have normal urinary and plasma epinephrine, norepinephrine levels and show normal response for epinephrine infusion and there is no evidence for increased catecholamine synthesis or metabolism at nerve endings.

Thyroid activity in foetus:

Thyroid hormone is important for fetal, as well as neonatal, brain development and nerve myelination. Thyroid hormone production rate per unit area is more in neonates and children than adults.

Congenital hypothyroidism occurs in babies if thyroid gland does not produce adequate thyroid hormones. Mental retardation is prevented if the hypothyroid child is treated within a year of life.

Effect of Hyperthyroidism on Cardiovascular System:

There is increased circulatory demands which causes modifications in cardiac functions. Cardiovascular alterations also results from the hypermetabolism and there arises a need to release the heat produced.

Thyroid hormones acts on cardiac cells by altering the action of pacemaker (sino-atrial node). It increases the myocardial oxygen utilization, coronary blood

flow and the systolic of the heart. Heart has 2 myosin heavy chain isoforms, α MHC and β MHC encoded by two genes located on short arm of chromosome 17.

In hyperthyroidism circulatory T3 enter cardiac myocytes combines with its receptors and enters the nucleus, causes enhanced transcription of α myosin genes- α MHC, β adrenergic receptors, G proteins, Na K ATPase and while it causes inhibition of transcription of β MHC, phospholamban, two types of adenylcyclase. Thus the cardiac contractility is increased²⁴.

Excessive thyroid hormone production increase the tissue utilization of oxygen, thereby increasing the metabolites which cause vasodilatation. Therefore there is increase in the blood flow, cardiac output and heart rate. Increased thyroid hormones, by increasing the enzymatic activity, increases the strength of the heart²⁵.

In our study, sympathetic noradrenergic system alterations with altered thyroid functions were studied in the subjects. Thyroid hormone variations on certain cellular mechanisms in the heart causes many cardiovascular abnormalities.

It is well established hyper dynamic cardiovascular state with low vascular resistance and high cardiac output exist in hyperthyroidism.

It is also associated with tachycardia, increased cardiac muscle oxygen consumption, increased left ventricular diastolic and systolic function, low systemic vascular resistance and increased prevalence of arrhythmias, decreased exercise performance, and increased risk of cardiovascular mortality.

Pulse pressure is increased due to decrease in diastolic pressure and increase in systolic pressure.

Heart Rate Variability as an index of Cardiac Autonomic activity:

Autonomic Nervous System can be assessed using HRV analysis. The cardiac rhythm influenced by sympathetic and parasympathetic dysfunction can be evaluated by the interbeat variations of R-R interval²⁶.

The spectral variation of the heart rate in the lower (LF) and higher frequencies (HF) has a significant relationship to sympathetic and parasympathetic activity, respectively.

An exaggeration of sympathetic nerve tone in cardiac activity induces tachycardia and reduces cyclical beat-to-beat variations, whereas increased parasympathetic nerve activity reduces heart rate and increases Heart Rate Variability.

These derangements in autonomic nervous system can be found out by HRV, and the HRV indices help us to assess the disease severity in hyperthyroid patients.

Effect of Autonomic nervous system:

The thyroid glands are regulated by both neural and endocrine hormones. Many ganglia contribute to the innervation of this gland. There are two divisions in the autonomic nervous system namely, sympathetic and vagal nervous systems. Both are antagonistic in their target actions. Cardiac inotropic effects are partly due to adrenergic stimulation.

The increased sensitivity of atria to beta-adrenergic agonists is due to increased beta-adrenoceptor density and sympathetic stimulation on the β_1 receptors in the heart causes increase in the heart rate and cardiac output of hyperthyroid patients .

Thus increased thyroid hormones increases β adrenergic receptors, and sympathetic activity on beta receptors which is mainly via adenylyl cyclase-cyclic AMP. The cardiovascular derangements mostly get reversed by antithyroid treatment and normal thyroid function can be restored after some time.

II. AIM AND OBJECTIVES

PRIMARY AIM:

To investigate a possible relationship between hyperthyroidism and autonomic imbalance in hyperthyroid patients using spectral analysis of HRV.

SECONDARY AIM:

- To compare HRV of hyperthyroid and normal volunteers.
- To assess the cardiovascular risk in hyperthyroid patients using HRV.

OBJECTIVE:

1. To compare HRV analysis between hyperthyroid and normal volunteers.
2. To study the type of autonomic imbalance in patients who are hyperthyroid.
3. To study the sympathetic influence in hyperthyroid and its role in the pathophysiology of cardiac complications.

III.REVIEW OF LITERATURE

Autonomic Nervous System

The autonomic system has afferent nerves which carries information from viscera and the central processes enter spinal cord or brainstem.

Peripheral processes of afferents run with efferent nerves.

Word "autonomous" is taken from greek word the autos, meaning self and the nomos, meaning control. Thus autonomic nervous system is an involuntary system which controls the vegetative functions, so it is also called vegetative system.

An important function of autonomic nervous system is to maintain homeostasis. i.e, constant internal environment by releasing epinephrine, insulin and glucagon or renin, vasopressin Sympathetic and parasympathetic divisions are complementary in nature rather than antagonistic.

Autonomic nervous system has afferent neuron in dorsal root ganglia, connector neuron in the dorsal horn of grey matter, conducts impulse to the

ventral horn) and ventral horn cell which transmits the efferent impulses to skeletal muscle.

Sympathetic division can be considered as the accelerator i.e, it acts during fast responses flight or fight reactions and the parasympathetic division acts as the brake and functions during resting conditions eg. "feed and breed" ²⁷.

Both the divisions of autonomic nervous system carry visceral afferent and sensation information like vasomotor, respiratory, and viscera somatic reflexes and interrelated visceral activities²⁸.

ANS is responsible for activities of the organs of digestion, circulation, excretion, respiration, reproduction as well as sweat, lacrimal, salivary glands and adrenal medulla²⁹.

ANS relays between central nervous system and the visceral organs by the way of peripheral ganglia. Central neurons that contributes information to autonomic system has cell bodies located along an interrupted string of grey

matter in brain stem and spinal cord. Preganglionic sympathetic fibres causes release of epinephrine and nor epinephrine from adrenal medulla. Preganglionic Parasympathetic nerves go directly to vicinity of viscera .

Cells of origin of sympathetic division of the autonomic nervous system are located in lateral horn spinal grey matter from eighth cervical and 1st thoracic through 3rd lumbar segmental levels.

Autonomic Nervous System and Hypothalamus:

Th nerves from the hypothalamus projects to the parasympathetic vagal nuclei and other neurons in the medulla. Medulla also has a group of neurons that descend to the sympathetic system in the spinal cord .Withall these connections, the hypothalamus can control rate of the heart, cardiac functions, and vasoconstriction, ³⁰.

The suprachiasmatic nucleus project to the paraventricular nucleus of hypothalamus (PVN). The PVN and arcuate nucleus has TRH (thyroid releasing hormone) expressing neurons .

TRH is stored in median eminence from where it is released into the hypothalamo-hypophyseal portal vessels which reach the anterior pituitary³¹.

TRH acts on the basophils via adenylyclase - cAMP pathway and causes the release of TSH from the pituitary gland. Hypothalamus secretes TRH when the thyroid hormones secretion becomes low (negative feedback) and also by nervous stimuli like exposure to cold or stress³².

Autonomic Nervous System and Thyroid Gland:

The hypothalamo pituitary thyroid axis and neural control of the thyroid gland are the essential regulators of thyroid function. The autonomic nervous system derives from the neural crest which also gives rise to dorsal root ganglia.

The thyroid receive its sympathetic innervation mostly via superior cervical ganglion (SCGs). Jugular nodose ganglia and cervical dorsal root ganglia also supplies the thyroid gland.

Parasympathetic nerves via branches of superior laryngeal nerve and recurrent nerve, also supplies the thyroid gland

The thyroid nerve, which is a vagal branch, projects to the thyroid ganglion which has vasoactive intestinal peptide and neuropeptide Y expressing neurons³³.

Autonomic innervations to the thyroid gland may interfere with T_3 , T_4 concentrations by altering the thyroid responsiveness to TSH and also by interfering the deiodination of Thyroxine to Triiodothyronine by the Deiodinase enzyme.

Nuclear effects of thyroid hormone are delayed for 1 hour, which is the time taken for transcription and translation of specific enzymes or contractile proteins. Extranuclear effects may influence plasma membrane transport of calcium, sugar, and amino acids in addition to directly influencing mitochondria and are very rapid, occurring within minutes. It is possible that there exists an interaction between the adrenergic system and the thyroid hormone system, which may also contribute to the cardiac actions of thyroid hormone³⁴.

Hyperthyroidism challenges the adrenal function by decreasing the urinary excretion of 17-ketosteroids. Increased thyroid hormone effects are similar to those induced by epinephrine, including tachycardia, increased cardiac output and enhanced glycogenolysis, lipogenesis, and calorogenesis.

The relationship between graves ophthalmopathy, hyperthyroidism and thyroid dermopathy was ascertained and it was showed that thyroid dermopathy was seen in 13% of patients with graves ophthalmopathy ³⁵.

Some of the manifestations of thyrotoxicosis like eyelid retraction, tremor, excessive sweating and tachycardia are atleast partly alleviated by adrenergic antagonists.

Graves disease was first named after Robert Graves in 1835.He observed thyroid gland enlargement in patients along with palpitations, exophthalmos, pretibial myxedema ³⁶. Cardiovascular signs like increased heart rate, murmur, hyperdynamic precordium, abnormal heart sounds, ectopic beats and irregular rhythm were also associated.

Heart Rate Variability:

HRV has emerged as the common procedure to assess autonomic variations in humans for clinical studies from the last decade.

Autonomic nervous system can be evaluated by HRV is in the form of time-frequency representation ³⁷.

HRV is analysed from the interval between R-R waves. Many research articles have been published pertaining to HRV. Most commonly used spectral analysis method is fast fourier transformation(FFT) ³⁸.

The same is used in our study. The inputs and frequency components are analysed rapidly and the computation time can be reduced using FFT.

HRV can also be denoted as cycle length variability, RR Variability and RR interval tachogram. Cardiac function is good if the variability between RR interval is more. Cardiac mortality increases with sympathetic dominance and in parasympathetic inhibition. High-frequency domain decrease under acute pressure and emotional states ³⁹.

History of HRV:

HRV has a broad application in cardiology. Fifty years back , in Russia, the Science of heart rate variability was developed in one of the space program ⁴⁰.

HRV analysis is a excellent tool to depict the autonomic nervous system (ANS), because the HRV regulation is mainly from the sympathetic and parasympathetic nervous systems.

In 1965 the clinical application of HRV was first brought out by Hon and Lee ⁴¹ . He followed there is alterations in interbeat intervals before any appreciable change occurred in heart rate itself ,for example fetal distress.

In diabetics, the autonomic neuropathy RR interval is usually reduced . this was evaluated by Ewing ⁴² using a number of bed side tests

Wolf et al ⁴³, predicted that decreased heart rate variability is associated with increased risk of post infarction mortality in cardiac patients.

Akselrod et al ⁴⁴, developed heart rate variations analysis to investigate the interbeat differences in cardiovascular system.

Since the last five decades, different spectral analysis has been applied. Using Tachogram RR interval can be assessed . Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency .

Md Rasel Kabir, Noorzahan Begum ⁴⁵, found out that Hyperthyroidism is associated with altered cardiac autonomic nervous activity (CANA). Mean R-R interval was significantly lower but there is increased heart rate in untreated thyrotoxic patients. SDNN and RMSSD were significantly lower in untreated hyperthyroids. He concluded that decreased vagal modulation may be restored following adequate treatment.

V Cacciatori, F Bellavere et al ⁴⁶, conducted HRV analysis in hyperthyroid patients to study the autonomic balance . In his study, heart rate variability was evaluated in different conditions. The power spectral analysis during standing, lying and rest were measured by analyzing the power spectral density of heart rate cyclic variations. While performing autonomic function tests, reflex response of heart rate during lying to standing was higher in controls than hyperthyroid patients. He also performed valsava maneuver and deep breathing tests, which showed no differences in subjects. After methimazole treatment the altered cardiovascular parameters were restored, with slight predominance of the vagal tone in the thyrotoxic patients. Thus concluding that thyroid hormone excess may be the root cause for sympathetic dominance and sub normal vagal component.

Karthik S, Pal GK, Nanda N et al ⁴⁷, in his research, found autonomic imbalance in thyroid dysfunctions in various conditions like hyperthyroid, hypothyroid, normal females. Thyroid profile, body mass index, basal heart rate , blood pressure and spectral indices of HRV (TP, LFnu, HFnu and LF-HF ratio, mean RR, SDNN and RMSSD) were studied in all the subjects. Sympatho vagal imbalance was more prominent in thyrotoxic patients.

In all the subjects, LF-HF ratio was correlated with thyroid profile and he emphasized that the Sympathovagal imbalance was detected due to both vagal withdrawal and sympathetic overactivity and stressed on , to improve vagal the component in thyrotoxic subjects to attain autonomic equilibrium and homeostasis in cardiovascular system.

Tobaldini E, Porta et al ⁴⁸, conducted a research on heart rate variability (in a short term) with conditional entropy indices in hyperthyroid and euthyroid females. The study was conducted in different positions like standing, and rest. In both study groups, during standing, the mean heart period was reduced but there is no significant difference at rest. The low frequency power was elevated in thyrotoxic groups than the euthyroids. During standing, the respiratory rate and complexity was increased in the thyrotoxic group than the euthyroid groups. There is a significant complexity in cardiovascular function, which could be attributed to both sympathetic over activation and also to the increased metabolic effects of the elevated thyroid hormone levels.

Thyroid hormone stimulates the metabolic activities and increases the basal rate of oxygen consumption and heat production in most tissues except the brain, retina, gonads, lungs, spleen. Increase in resting metabolic rate found

in hyperthyroids is partly due to an increase in hepatic metabolism in liver cells.

Stuart Gordon recognised in his study that a patient may suffer from hyperthyroidism in the absence of a continually elevated metabolic rate, since the disease is characterised by remission and exacerbations, the basal metabolic rate can be normal or subnormal also and this occurs mainly in patients with nodular goitre and the degree of degenerations are more in nodular goiter⁴⁹.

Early in 1928, Clute suggested that there were patients with history, physical examination and investigations entirely consistent with hyperthyroidism, yet the basal metabolic rate is normal or subnormal⁵⁰.

During 1931, Plummer has placed on record of hyperthyroid subject having a basal metabolic rate of -9 but the normal basal metabolic rate can vary from -10 to 15. Thus proved that hyperthyroidism can occur with least possible basal rate⁵¹.

Chen JL, Chiu HW et al⁵², showed that autonomic imbalance state prevails in hyperthyroidism. It is characterized by both increased sympathetic and decreased vagal modulation of heart rate which is analysed from spectral analysis of heart rate variability. HF nu, LF nu, VLF, HF, LF, Total power were

analysed in the study groups. (LF/HF) Ratio an low frequency is increased in hyperthyroids than controls. After antithyroid treatment, HRV parameters were gradually brought back to normal levels like those of the controls. The study brought out relationship between HRVparameters and the thyroid function tests.

Burggraaf J, Tulen JH, et al ⁵³, suggested that there is Sympathovagal imbalance in hyperthyroidism. In thyrotoxic cases, HF parameters are decreased along with SDNN parameters. This proves diminished resting parasympathetic inputs to the cardiovascular system . Raised urinary levels of epinephrine and norepinephrine clearly depicts the enhanced sympathetic activity in the cases. Thus both the craniosacral and thoraco lumbar outflow are deranged causing variations in heart rate.

Girard A, Hugues FC et al ⁵⁴, computed the HRV analysis by studying the variability of blood pressure and heart rate in thyrotoxic cases. It showed a fall in HF parameters. Overall heart period variability is decreased in the cases than the controls in the supine position. There is a clear deficit in the orthostatism-induced mid-frequency systolic blood pressure rise in the hyperthyroid state compared with the euthyroid state. Significant decrease in vascular response to standing is elicited .

Barczy M, Tabor S, Thor P et al⁵⁵, studied the sympathovagal system with heart rate variability analysis in hyperthyroid patients . Reduction of RR intervals, increase of LF and HF ratio and in decrease of SDNN in hyperthyroidism. After attaining pharmacological euthyroidism and surgical euthyroidism, there were increase in RR intervals, reduction of LF/HF ratio and increase of SDNN in comparison to hyperthyroidism .

Jin Long Chen et al⁵⁶, suggested that hyperthyroid patients and normal controls could be distinguished by correlation dimension of heart rate variability. He found that there is reductions in the R–R interval in cases than controls .Also there is reduced correlation dimension in hyperthyroid patients . This depicts the reduced complexity and decreased tolerance to cardiovascular stresses in thyrotoxic subjects. Thus this is the reason for exercise intolerance and anxiety, irritability in hyperthyroid patients.

Osman, F and Franklyn et al⁵⁷, assessed time-domain parameters and heart rate turbulence (HRT) in severe thyrotoxicosis subjects . Measurements of HRT (onset and slope) decreased in patients with overt hyperthyroidism, but following antithyroid treatment , the slope is restored to normal values with antithyroid treatment .

1991, President George Bush had tachycardia and was diagnosed with atrial fibrillation, which is usually seen in older individuals with high blood pressure, coronary artery disease, valves dysfunction. He was not known to have these problems, but after medical evaluation, he was found to have Graves' disease. Atrial fibrillation was found in 25% of individuals who had developed hyperthyroidism over the age of sixty⁵⁸.

Massimo Casu, et al⁵⁹, analyzed the sympathetic and parasympathetic control of heart rate variability (HRV) in the population who had undergone thyroidectomy and later supplemented with Levo -thyroxine and I¹³¹ therapy for thyroid carcinoma. Systolic and mean Blood Pressure were elevated in hyperthyroids. Decreased sympathetic tone with preserved vagal tone, was detectable in patients with hyperthyroxinemia after getting thyroxine treatment. Gradual restoration of increased systolic and mean blood pressure but not diastolic BP.

Frans Brandt⁶⁰ showed that severe hyperthyroidism was associated with coagulation disorder, rhythm disturbances, hemiplegia, and vascular embolism. Incidence of Cardiovascular morbidity and mortality in hyperthyroid patients increased to 20%.

Marcus Dörr ⁶¹ studied the relationship between function of the thyroid gland ,Left Ventricular hypertrophy, cardiac muscle mass . Decreased serum thyroid hormone levels and thyroid stimulating hormone levels predict cardiovascular mortality, which could be described by left ventricular hypertrophy (LVH).

Tremendous burden is imposed on the heart in hyperthyroidism. In such patients, even at rest the working capacity of the heart is so great as the normal heart, when undergoing the most strenuous exercise and if it is allowed to continue, myocardial reserve will decrease and myocardial damage will occur eg. Cardiac hypertrophy.

Subclinical hyperthyroidism could be the cause for increased risk of atrial fibrillation and cardiac mortality, osteoporosis in women of postmenopausal age group.

The study by Kaminski suggests that subclinical hyperthyroidism when compared to normal thyroid status may be associated with a statistically significant increase of QT interval dispersion. In subclinical hyperthyroidism, prevalence of increased ventricular extra systole, increased arterial blood Pressure, and changes in Heart rate variability like mildly elevated LF parameters are appreciated ⁶².

Hartong R, Wang N et al ⁶³, suggested that thyroid hormone T3 regulates gene transcription of the Ca-ATPase in the sarcoplasmic reticulum. So increased thyroid hormone responsiveness is pronounced .

Eric Oetter ⁶⁴ conducted a Heart Rate Variability Research .He found out whenever body is confronted with stress conditions, there is decreased variation between beats. This is suggestive of overt activity of sympathetic nervous system .The “fight-or-flight” response come in to action to maintain homeostasis. When the body assumes resting condition, the heart rate variability increases, indicating the increase in the parasympathetic tone of the autonomic system.

Atrial fibrillation, cardiomyopathy, sinus arrhythmia, mitral stenosis, mitral valve prolapse , cardiac failure are the different types of cardiac pathology in hyperthyroid patients diagnosed from echocardiography, chest radiograph and electrocardiography.

Anne R. Cappola, M, showed that thyroid dysfunction is associated with increased prevalence of cardiovascular risk. The study was conducted in people above 65 years and TSH was tested. 82 % of the study population showed euthyroid status.15 % were known to have subclinical hypothyroidism .1.6% suffered from hypothyroidism, and 1.5 % had

subclinical hyperthyroidism . Subjects with subclinical hyperthyroidism had twice the risk of developing atrial fibrillation when compared to the people with normal thyroid function ⁶⁵ .

Hyper active thyroid gland is linked with an increased risk for atrial fibrillation (a type of abnormal heart rhythm) . But the normal or under active thyroid gland has lower risk for cardiovascular problems or death⁶⁶.

Simply the presence of high thyroxine levels in euthyroid patients of 60 years or older was known to have three times higher risk in developing atrial flutter or fibrillation ⁶⁷ .

Barczyński M et al ⁶⁸ estimated sympathetic and parasympathetic function in hyperthyroids by the spectral analysis of heart rate variability and evaluated the impact of pharmacological and surgical treatment on the ANS function. Statistical significance was found in reduction of range of RR intervals, in increase of LF/HF ratio and in decrease of SDNN in hyperthyroidism in comparison to the control group .Pharmacological therapy with thyreostatics and surgical treatment can normalizes autonomic nervous system to the control group level.

Thirtysix years of follow-up of hyperthyroidism indicate that Left Ventricular hypertrophy is reversible and reversal towards euthyroid status

provides significant benefit for the anatomical manifestations of Left ventricular hypertrophy. Incidence of left ventricular hypertrophy and cardiovascular morbidity were found to be different in the cases. This is because, the cardiovascular health is also assessed by glucose intolerance, high blood pressure, lipid profile alcohol and smoking ⁶⁹.

Noh JY, Nakamura Y et al⁷⁰ studied Sympathetic overactivity occurs in Graves' disease, but little is known about autonomic nervous function in their eyes They examined this function of the intraocular muscles in 12 patients with hyperthyroid Graves' disease and 12 controls. Pupil size, pupillary unrest, and The mean pupil size of the patients was not different from that of the controls. Pupillary unrest and Accommodation in the patients was lower than that of the controls.; pupillary unrest and accommodation had improved in all five patients. These results indicate that intraocular muscles are sympathetically overactive in hyperthyroid patients .

Cavallo A ⁷¹, in his research, discovered unusual cardiac manifestations in few of hyperthyroid patients like transient apical systolic murmur , persistent cardiomegaly, and the remaining had persistent apical systolic murmurs and cardiomegaly, mitral regurgitation and congestive heart failure. Persistent and

severe cardiac morbidity occurred only in long standing cases ,because of the poor compliance with antithyroid treatment

Thomas Seepal⁷² assessed the metabolic effects of untreated hyperthyroids and untreated hypothyroids by using Bioelectrical whole body resistance (R) and reactance (Xc) for calculating the lean body mass, body cell mass (BCM), extracellular mass (ECM) and body fat . ECM/BCM ratio was elevated in all hyperthyroid subjects due to a loss of muscle mass and due to an increase in extracellular fluids but in hypothyroidism there is decrease in ECM/BCM .Body composition variation could not be evaluated from the thyroid dysfunction . and he showed that BIA detects small metabolic manifestations in thyroid dysfunction.¹⁰⁵ .

Loss of weight and increase in weight was observed in thyrotoxic patients . In these patients, serum ghrelin levels measured in before and during treatment .It was found that fasting serum ghrelin concentration was significantly reduced in the women with hyperthyroidism than in the normal women but it increases after antithyroid drug treatment. Also the hyperthroid individuals had less body mass and reduced fat tissue than the euthyroid women. Following treatment, the body mass

and weight can be increased significantly.

Lozano HF⁷³, studied a case of Graves disease with congestive cardiac failure, tricuspid regurgitation with elevated pulmonary venous pressure. All these complications slowly disappeared as soon as the treatment is initialised. Release of increased pulmonary vasodilators, high output failure and endothelial injury induced are all well known etiology for the emergence of autoimmune activity and pulmonary hypertension. Thus any unexplained cardiac failure and elevated pulmonary vascular resistance could be due to hyperthyroidism and all the complications are treatable entities.

IV. MATERIALS AND METHODOLOGY

This research study was carried out in our physiology laboratory, after getting ethical clearance from the institutional human ethics committee and informed consent from the subjects, in both hyperthyroid and control groups.

The period of study was nine months.

INCLUSION CRITERIA:

- Age between 30-50 yrs.
- Body Mass Index- Between 18.5 to 25.
- Both males & females who are Physically active.
- Newly diagnosed 30 hyperthyroid patients with TSH less than 0.27 micro IU/ml
- 30 normal volunteers with TSH normal range .

EXCLUSION CRITERIA:

- Hypertensives.
- Diabetics.
- Patients on regular or irregular anti thyroid treatment.
- The subjects who were on drugs affecting Autonomic Nervous System like anticholinergics, digoxin, minoxidil, theophylline, sympathomimetics, phenobarbitone.
- Females who were psychiatric patients.
- Those who were having BMI more than 25 and less than 18.5

STUDY POPULATION

- Newly diagnosed hyperthyroid patients (before starting treatment) attending Medical Out Patient department and normal volunteers.
- After getting clearance from Institutional Human Ethics Committee (IHEC) and Department of Clinical Research and Bioethics (DCRB) the subjects who fulfilled the criteria for study were taken for ECG recording and HRV analysis.
- Thyroid Function Test reports, Age in years, Height in cms, Weight in kilograms of both Hyperthyroid and normal volunteers were collected.

- A detailed history taking and a complete physical examination was done and a complete record was obtained for future verification.

ANTHROPOMETRY

Body Mass Index

All the subjects were measured for height and weight. From this BMI was obtained by dividing weight in kilogram by square of the height in meters.i.e,

$$\text{BMI} = \frac{\text{weight in kilogram}}{\text{height in meter square}}$$

BMI of 18.5 to 24.9 kg/m² were graded as normal, 25 to 29.9 kg/m² were graded as overweight and more than 30 as obese. Only the participants with normal BMI were included in the study

BASAL METABOLIC RATE

It is defined as the rate of calorie consumption in the post absorptive state ,in the absence of any muscular activity, at a comfortable environmental temperature and with the patient resting comfortably.

The thyroid hormone is one of the determinant of energy expenditure ,basal metabolic rate and thermogenesis . Many studies have showed the effects of thyroid hormone on cell metabolism ,involved with energy expenditure. But It is not clear whether 3,3'-triiodothyronine dependent metabolism are most relevant for the evaluation of BMR .

BMR is affected by various factors like gender, age, degree of work , thyroid hormones, body temperature, nutritional state, pregnancy, caffeine and tobacco use, growth and development.

BMR can be responsible for burning up to 70% of the total calories expended.

Metric BMR Formula

Women: **BMR** = $655 + (9.6 \times \text{weight in kilos}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age in years})$

Men: **BMR** = 66 + (13.7 x weight in kilos)+(5 x height in cm) - (6.8 x age in years)

THYROID FUNCTION TESTS:

In the recent days highly precise thyroid function tests are there to establish a diagnosis of hyperthyroidism. The thyroid gland synthesise levothyroxine (T₄) and triiodothyronine (T₃) which is based on the negative feed back loop. The thyroid hormone dysfunction can be studied by TSH assay which is highly sensitive . Immunoassay which we used for in vitro quantitative determination of T3, FT4,TSH, FT3 is **ECLIA** (ELECTRO CHEMI LUMINESCENCE IMMUNO ASSAY) . This method has been validated for determination of plasma thyroid harmones in human samples and commonly are used in medical diagnostic Laboratories.

T3 and FT3 assay employs a competitive test principle with polyclonal antibodies. Direct measurement of FT4 , FT3 via equilibrium dialysis or ultrafiltration is mainly used as a reference method for standardizing the immunological procedures used for routine diagnostic purposes.

Free T4 is measured together with TSH , when thyroid function

disorders are suspected . TSH is a glycoprotein and consists of two subunits, the alpha and the beta subunit.

- The α (*alpha*) subunit is nearly identical to that of human chorionic gonadotropin (HCG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH)⁷⁴ . The α subunit is responsible for stimulation of adenylyl cyclase and generation of Cyclic AMP.
- The β (*beta*) subunit determines its biological receptor specificity and it is unique to TSH.

TSH assay is a screening test and confirm thyroid disorders and to follow the treatment response.

Reference range:

TSH - 0.27 to 4.2 micro IU/ml

FT4 - 0.932 to 1.71 ng/dl

FT3 - 2 to 4.4 pg/ml

T3 - 0.846 to 2.02 ng/ml

Cases and controls were selected based on this test .

Subjects whose TSH values less than 0.27 are taken as cases.

The volunteers whose thyroid function tests in the normal range are taken as controls.

HRV analysis is done before starting antithyroid treatment in the cases.

ECG RECORDING AND HRV ANALYSIS

HRV is a non invasive procedure. Recording electrocardiogram for 10 minutes in a computerized physiograph (NEVIQURE-Digital ECG recorder) in Lead II and analysis by using Finland software.

ECG Recording

Informed consent was taken from all the subjects before taking ECG. In the research laboratory, the subjects were asked to take rest(i.e, lying quietly in the supine position on the couch, awake and not making any movements) for 5 minutes before the procedure, so as to alleviate unnecessary anxiety and they were also made aware about the ECG procedure.

ECG was recorded using the computerized physiograph Inco digital ECG recorder in lead II for a period for 10 minutes by placing disposable adhesion electrodes on the pattern of lead II configuration .

Positive electrode was connected to left arm, negative electrode to right arm, reference electrode on left foot and ground electrode on right foot. Baseline electro cardiogram were taken from the study population and the subjects with abnormal baseline ECG were excluded.

RR intervals were obtained after clearance of noise and baseline fluctuations by digital filters. Those who had ectopic beats were excluded from the study. Resting heart rate is also recorded. The datas were filtered using a digital notch filters with a sampling rate of 1000 samples/sec.

The inbuilt software selected the RR peaks and these RR intervals which were obtained as time points were then fed in to a Microsoft excel sheet and RR intervals were copied to a notepad file.

HRV analysis was done by feeding this RR intervals notepad file.

The resting autonomic activity was assessed by measuring the 10 minute heart rate variability and HRV indices determined are

The Time domain parameters calculated are :

- **Mean RR(NN)**

This is the average of all NN intervals. At a given physiological state it varies inversely with mean heart rate, this also indicates sympatho vagal balance .

- **SDNN**

It is the standard deviation of all NN intervals.

It is a measure of total variability. When considered for a short time period, it reflects HRV in low and high frequency ranges.

- **NN50**

It is the number of pairs of adjacent NN intervals differing more than 50 ms.

- **PNN50**

It is the proportions of NN50 divided by total number of NNs. This is also an estimate of high frequency variation in heart rate.

- **RMSSD**

The square root of the mean of the sum of the squares of differences between adjacent NN intervals .This is an estimate of high frequency variations in heart rate and hence a measure of vagal modulation.

Frequency-domain measures:

It shows the HRV at few frequency ranges CORELATING WITH CERTAIN physiological processes. All the abnormal beat-beat variations and artifacts were analysed and removed. Tachogram of RR intervals must be sequentially taken to make it regularly sampled signal

A routine spectral analysis is applied to our modified recording and all the time and frequency domain parameters are analysed on 10-minutes time interval.

Frequency domain parameters calculated are:

- **Low frequency power(LF)** –It is taken in the range from 0.04 to 0.15 Hz .This power depicts both the divisions of autonomic nervous system .
- **High frequency power-** It is taken in the range from 0.15 to 0.4 Hz. This power depicts vagal tone.
- **LF norm (nu)** - Low frequency power in normalized units.
$$\text{LF}/(\text{Total power} - \text{VLF}) \times 100$$
- **HF norm (nu)** – high frequency power in normalized units.
$$\text{HF}/(\text{Total power} - \text{VLF}) \times 100$$

- **LF/HF power ratio-** It is used to depict the sympathovagal imbalance .increase in this ratio usually depicts vagal inactivity and sympathetic dominance .

HRV analysis was done by feeding this Harmonic components of RR interval notepad file to HRV analysis software version 1.1 from Biomedical Signal Analysis group, Department of Applied Physics , University of Kuopio, Finland

Power spectral analysis was done by fast fourier transformation, discovered by Jean Baptiste Joseph Fourier.

Statistical analysis

The statistical analysis was done using SPSS software (statistical package for the social science version- 19) By independent Students t' test, Analysis was done between the study group and control group. Both HRV and Thyroid hormone levels were compared, which gave the exact relationship between HRV and increased T3, T4 and decreased TSH levels.

Values are expressed as Mean \pm SD.

P <0.05 was considered to be statistically significant.

POWER SPECTRUM OF HRV

PC display of the HRV analysis software version 1.1

The LF/HF ratio was expressed as the ratio of the normalized areas, calculating the ratio of the percentage power contained in the LF band to that in the HF band.

Mean heart rate, LF/HF power ratio, individual LF and HF area power, and normalized area were individually measured in all subjects for all experimental conditions.

V. RESULTS

60 patients were subjected to ECG recording. 30 patients were newly diagnosed hyperthyroid patients before starting treatment and 30 patients were euthyroid. 10 minute Electro cardiogram was taken for all the 60 patients and HRV analysis was done.

The HRV parameters (Time domain measures and the frequency domain measures) were compared between the cases and controls.

Both HRV and thyroid hormone levels were compared, which gave the exact relationship between HRV and increased T3, T4 and decreased Thyroid Stimulating Hormone (TSH) levels.

ANALYSIS BETWEEN CASE AND CONTROLS.

1. Baseline characteristics of the Hyperthyroids and normal volunteers

Results are expressed as Mean \pm SD.

Age (in yrs)

Mean age of the Hyperthyroids was 39.23 ± 6.91 and the Euthyroids was 42.13 ± 6.78 . There was no significant difference between ages with p value 0.140.

Height (in cms)

Height of Hyperthyroids was 160.40 ± 6.52 and Euthyroids was 159.27 ± 7.58 . There was no significant difference in weight between these groups with p value 0.551 .

Weight (kgs)

Weight of Hyperthyroids was 58.50 ± 6.21 and Euthyroids was 59.03 ± 7.02 . There was no significant difference in weight between these groups with p value 0.781.

BMI (kg/m²)

BMI of the Hyperthyroids was 22.70 ± 1.64 and the euthyroids was 22.86 ± 1.28 . There was no significant difference between BMI with p value 0.671.

2. Resting Heart rate and BMR of the Hyperthyroids and normal volunteers

Resting Heart rate (RHR per min)

RHR of the hyperthyroids was 97.67 ± 17.71 and euthyroids was 74.47 ± 5.34 and the p value < 0.001 (extremely significant)

Basal Metabolic Rate (BMR)

BMR of hyperthyroids was 1348 ± 122.88 and euthyroids was 1332 ± 117.48 and the p value 0.641.

3. Comparison of frequency domain measures of the Hyperthyroids and normal volunteers

Low power frequency in normalized units(LF n.u)

LF of the Hyperthyroids was 78.99 ± 10.38 and Euthyroids was 50.99 ± 12.23 and p value < 0.0001 (extremely significant).

High power frequency in normalized units (HF n.u)

HF of the Hyperthyroids was 21.47 ± 9.96 and Euthyroids was 48.98 ± 12.24 and p value < 0.0001 (extremely significant)

LF/HF ratio

LF/HF of the Hyperthyroids was 4.81 ± 2.81 and Euthyroids was 1.17 ± 0.57 and p value < 0.0001 (extremely significant).

Low power frequency (LF) power %

LF of the Hyperthyroids was 31.333 ± 12.68 and euthyroids was 26.213 ± 9.71 and p value of 0.070 (significant).

High power frequency (HF) power %

HF of the Hyperthyroids was 8.49 ± 7.66 and euthyroids was 28.39 ± 13.99 and p value < 0.0001 (extremely significant).

Very Low power frequency (LF) power %

LF of the Hyperthyroids was 59.11 ± 21.098 and the Euthyroids was 46.35 ± 18.35 and p value of 0.008 (significant).

4. Comparison of time domain measures of the of the Hyperthyroids and normal volunteers

Mean RR(s)

Mean RR of the Hyperthyroids was 0.62 ± 0.11 and the Euthyroids was 0.77 ± 0.062 . There was significant difference between the Mean RR of both the groups with $p \text{ value} < 0.0001$ (extremely significant).

RMSSD

RMSSD of the Hyperthyroids was 14.19 ± 7.69 and Euthyroids was 38.66 ± 7.66 and p value of <0.0001 (extremely significant).

NN 50(count)

NN 50 of the Hyperthyroids was 8.67 ± 8.07 and Euthyroids was 79.67 ± 17.34 and p value <0.0001 (extremely significant).

pNN₅₀ (%)

pNN₅₀ of the Hyperthyroids was 4.30 ± 4.02 and Euthyroids was 21.46 ± 12.53 and p value < 0.0001 (extremely significant)

SDNN(ms).

SDNN of the Hyperthyroids was 24.297 ± 12.359 and Euthyroids was 39.67 ± 8.625 and p value < 0.0001 (extremely significant).

5. Comparison of TFT (ELECSYS IMMUNOASSAY) of Hyperthyroid and Euthyroid groups.

SERUM TSH (in μ IU/ml)

Mean TSH of the Hyperthyroids was 0.017 ± 0.019 and Euthyroids was 2.09 ± 0.062 with p value < 0.0001 (extremely significant).

T₃ (in ng/ml)

T₃ of the Hyperthyroids was 2.94 ± 1.71 and Euthyroids was 1.20 ± 0.175 and p value < 0.001 (significant).

FT₄ (in ng/ml)

FT₄ of the Hyperthyroids was 2.91 ± 1.97 and Euthyroids was 1.11 ± 0.18 and p value < 0.0001 (extremely significant).

FT₃ (in Pg/ml)

FT₃ of the Hyperthyroids was 7.33 ± 6.75 and Euthyroids was 2.09 ± 0.85 and p value < 0.001 (significant)

1. Comparison of Baseline characteristics of Hyperthyroid and Euthyroid

groups

Table-1

Parameter	Group	Mean±SD	P Value
Age(yrs)	Cases	39.23± 6.91	0.140 (NS)
	Controls	42.13± 6.78	
Height	Cases	160.40± 6.52	0.551 (NS)
	Controls	159.27± 7.58	
Weight	Cases	58.50 ± 6.22	0.781(NS)
	Controls	59.03± 7.02	
BMI(kg/m²)	Cases	22.70± 1.64	0.671 (NS)
	Controls	22.86 ± 1.29	

NS- Not significant

*** Significant**

**** Very significant**

***** Extremely significant**

2. Comparison of Resting Heart rate and BMR of the Hyperthyroids and Euthyroid groups

Table-2

Parameter	Group	Mean±SD	P Value
RHR	Cases	97.67±17.71	<0.005**
	Controls	74.47± 5.34	
BMR	Cases	1348± 122.88	0.641 (NS)
	Controls	1332± 117.48	

NS- Not significant * Significant ** Very significant

3.Comparison of Frequency domain measures of Hyperthyroids &Euthyroids

Table-3

Parameter	Group	Mean \pm SD	P value
LF nu	Cases	78.996 \pm 10.383	<0.0001***
	Controls	50.993 \pm 12.226	
HF nu	Cases	21.466 \pm 9.965	<0.0001***
	Controls	48.983 \pm 12.240	
LF/HF ratio	Cases	4.8150 \pm 2.811	<0.0001***
	Controls	1.174 \pm 0.5721	
LF power	Cases	31.33 \pm 12.683	<0.0001***
	Controls	26.21 \pm 9.710	
HF power	Cases	8.496 \pm 7.669	

	Controls	28.396±13.985	<0.0001 ^{***}
VLF power	Cases	59.114±21.098	<0.0001 ^{***}
Parameter	Controls Group	46.350±18.356 Mean ±SD	P value

NS Not significant * Significant ** Very significant *** Extremely significant

4. Comparison of time domain measures of Hyperthyroids and Euthyroids

Mean RR(s)	Cases	0.621±0.106	<0.0001 ^{***}
	Controls	0.769±0.062	
SDNN(ms)	Cases	24.297±12.36	<0.0001 ^{***}
	Controls	39.675±8.63	
RMSSD	Cases	14.196±7.69	<0.0001 ^{***}
	Controls	38.656±7.66	
NN50(count)	Cases	8.67±8.07	<0.0001 ^{***}
	Controls	79.67±17.35	
pNN50(%)	Cases	4.30±4.0	<0.0001 ^{***}
	Controls	21.46±12.53	

Table-4

NS Not significant ***** Significant ****** Very significant ******* Extremely significant

5. Comparison of TFT (ELECSYS IMMUNOASSAY) of Hyperthyroid and Euthyroid groups.

Table-5.

serum	Normal range	Group	Mean \pm SD	P value
TSH (μ IU/ml)	0.27-4.2	Cases	0.017\pm0.019	0.0001^{***}
		Controls	2.091\pm0.853	
T3 (ng/ml)	0.846-2.02	Cases	2.938\pm1.71	0.001^{**}
		Controls	1.202\pm0.175	
FT4 (ng/dl)	0.932-1.71	Cases	2.908\pm1.97	0.0001^{***}
		Controls	1.108\pm0.177	
FT3 (pg/ml)	2-4.4	Cases	7.33\pm6.747	0.001^{**}
		Controls	2.091\pm0.853	

NS Not significant ***** Significant ****** Very significant

******* Extremely significant

VI. DISCUSSION

Thyroid hormones modulates the development, growth and metabolism of each and every system in our body .Hyperthyroidism is due to hyperactive thyroid gland and increased production of thyroid hormones T3 , T4 and decreased serum TSH.

Hyperthyroidism frequently presents with tachycardia, palpitations and widened pulse pressure. Cardiac contractility and cardiac output is immensely elevated in hyperthyroids due to the additive effect of elevated ejection fraction, resting heart rate, and blood volume with a decrease in diastolic function. Sympathetic nervous system activation and thyrotoxicosis manifestations are mostly similar, especially in the inotropic effects

The thyroid hormone receptor isoforms alpha and beta are bound to the oligomer within the retinoid X receptor. α - MHC predominates in the atria of adults⁷⁵.

Recent studies in heart showed that thyroid hormones especially cause enhanced gene transcription of the calcium ATPase in sarcoplasmic reticulum and increase the pacemaker activity in cardiac cell

Thyroid hormone has its effect on duration of cardiac pacemaker potential and repolarization currents. It alters both non genomic and genomic actions and the net effect is to alter the heart function towards increased contractility⁷⁶.

It is possible that there exists an interaction between the adrenergic hormones and the thyroid hormones, which may also contribute to the cardiac actions of thyroid hormone⁷⁷.

A study done by Williams showed that thyroid hormones increase sensitivity to β -adrenergic agonists by increasing the β -adrenoceptor density and G_s/G_i protein ratio with an excess activation of the adenylate cyclase⁷⁸.

HRV is the good marker for identifying the cardiovascular risk and severity in hyperthyroids. HRV denotes the individuals autonomic tone and Frequency domain measures are considered to be best semiquantitative method for parasympathetic and sympathetic activity.

Increase in sympathetic tone in cardiac pacemakers induces tachycardia and reduce HRV, whereas increased parasympathetic activity causes bradycardia and increases beat to beat differences.

Higher HRV is always desirable and Lower Heart Rate variability is an established marker of cardiovascular deaths and complications . Abnormal variability also predicts the cardiovascular etiology for mortality, coronary atherosclerotic development and cardiac arrhythmias.

In this study population, cases showed decreased HRV parameters. Of the HRV parameters, frequency domain measures HF power, HF nu was less among patients than controls. This clearly depicts that parasympathetic activity is less among hyperthyroid patients.

Thyroxine hormone increase the body temperature and produce vasodilatation. This increase the cutaneous circulation. But decrease in the peripheral resistance with decrease in diastolic blood pressure.

There is decrease in the circulation time, due to increase in the blood flow velocity. In spite of increased cardiac output, there is less tissue perfusion ,thus causing dyspnea in high output cardiac failure.

LF nu, and LF power and LF/HF Ratio were high among hyperthyroids than controls. This shows that sympathetic activity is high in hyperthyroid patients and it is consistent with the study done by chiu HW and chen JL who emphasized that hyperthyroidism is characterized by an abnormal increase in sympathetic and decrease in vagal activity in heart.

So the sympathetic to vagal ratio may increase in Hyperthyroids. But few young Euthyroid patients (with normal TFT), have LF/HF ratio more than 1, showing little sympathetic dominance, which can be due to stress. However it is negligent when compared to hyperthyroid patients with enormous hike in LF/HF ratio.

In our study, basal metabolic rate is elevated in few hyperthyroid patients than the controls. By Calculating the BMR it is clear that BMR elevation is directly proportional to the increase in T_3 , T_4 and LF. (Low frequency domain measuring sympathetic activity) .This relationship is well brought out in our study than the previous studies. But there are few hyperthyroid patients, who had normal BMR. This depicts all hyperthyroid patients need not have elevated BMR.

Of the time variables, mean RR interval, p NN 50 and NN50 were less among the patients than controls, relating to the parasympathetic withdrawal.

Similarly SDNN and RMSSD were significantly lower in untreated hyperthyroids than euthyroids. This shows that high frequency variations in heart rate are less and vagal modulation of the autonomic nervous system is decreased.

A certain number of cases showed NN50 and pNN50 equals 0. It emphasizes that adjacent NN intervals differing by more than 50ms is zero. So the high frequency variations in heart rate in these patients were zero. Thus the vagal activity is least. These patients are high risk patients for cardiovascular complication like atrial fibrillation and arrhythmias. Our study is of great relevance in this aspect.

Supraventricular arrhythmias, atrial fibrillation, cardiac failure are the known cardiovascular complications of thyrotoxicosis and the same was proved to be the primary cause of death.

There is an association between thyroid gland function, heart muscle mass, and ventricular hypertrophy. Hyperthyroidism is an independent risk factor for LVH.

In the geriatric age group, the TSH levels are low, and the preponderance for atrial fibrillation and right heart failure is twice than that of middle aged people.

Left Ventricular Hypertrophy has emerged as an important marker of progressing atherosclerotic processes which can be appreciated by ECG, ECHO or X-ray and Cardiovascular complications proportionately increase with increasing left ventricular muscle mass .

TSH values were significantly reduced in hyperthyroids. TSH has a linear relationship with parasympathetic activity. T3, T4 were immensely elevated, which is directly proportional with sympathetic activity and the degree of vagal withdrawal. This relationship is well brought out in our study than any other previous studies.

Our study gives a solid and strong evidence of increased cardiac autonomic activity –showcasing the sympathetic dominance as the culprit for all cardiac morbidity and mortality.

With the help of our HRV analysis in hyperthyroids, patients who are at risk for cardiac complications are found out using the time and frequency domains and early intervention can be done to prevent mortality rates.

β -adrenergic blockers (β 1-selective or nonselective agents)could be suggested for high risk cases as an initiative measure. Tachyarrhythmias can be converted to sinus rhythm patterns and normal conducting patterns can be

obtained by radioactive iodine, antithyroid drugs and thyroidectomy. It all needs a brief period of time to bring it to normal cardiovascular status.

LIMITATIONS OF THE STUDY

Few limitations observed are,

1. Sample size of the study can be more.
2. It is difficult to get patients before starting anti thyroid treatment.

VII. Conclusion

To our knowledge , this is the first study to investigate the autonomic innervations of the heart in thyrotoxicosis subjects using HRV analysis and comparison of BMR between the case and control groups.

The results of our study show that there is reduced parasympathetic component and elevated sympathetic component in hyperthyroid patients. The cause is found to be the reduced levels of TSH levels as well as the increased thyroid hormones.

In the view of present study results, disturbances of sympathetic branch of Autonomic Nervous System can be observed in patients with thyrotoxicosis.

A predominance of sympathetic tone has cardio acceleratory effect and reduced beat-to-beat variations and therefore causes positive inotropic effects.

Reduced Heart Rate variability is most commonly linked with a risk of arrhythmic death and it is the independent predictor of cardiac mortality and morbidity, but recent data suggests that any abnormal variability also predicts circulatory dysfunction, progression of coronary atherosclerosis and death due to arrhythmias.

The beta adrenergic blocking drugs reduce both cardiovascular and central nervous symptoms. It helps to reduce the anxiety while preparing patients for surgery.

Beta-adrenergic blockers slow the resting heart rate from 97 to 80 beats/min and bring the rate of diastolic deceleration to normal .

Beta blockers are usually prescribed to reduce the symptoms of thyrotoxicosis such as tachycardia , palpitations, tremors, anxiety. Anti-thyroid treatment given to decrease the synthesis of thyroid hormones , particularly, in the case of Graves' disease .

We conclude that decreased vagal modulation on heart rate may occur in hyperthyroidism, which may be restored following adequate treatment of the disease by blocking beta receptors and there by inhibiting the adenylyl cyclase-cyclic AMP pathway.

This provides an attractive future option for management of arrhythmias and other cardiovascular complications due to thyrotoxicosis.

From our study it is obvious that cardiovascular risk in thyrotoxicosis patients can be evaluated by our HRV analysis before any appreciable change occurred in heart rate itself. Prevention is better than cure. So even before the appearance of cardiac complications, they can be assessed and halted.

Many randomised control trials can be done to bring out the unexplored effects of autonomic dysfunction on cardiovascular system. Thus cardiac morbidity can be assessed and treated earlier and mortality can be prevented using our HRV analysis.

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