HYPOTHYROIDISM AND CARDIAC ARRHYTHMIAS

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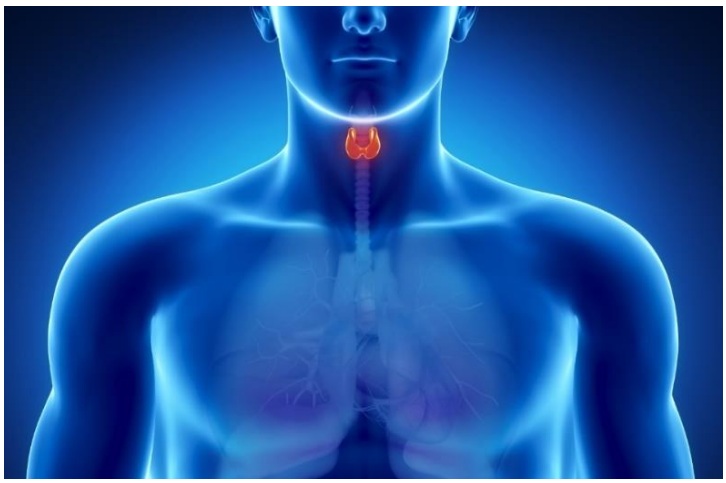
A Doctor of Philosophy (PhD) dissertation



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Poznań, 2017

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS:

A - amper
AC - adenylyl cyclase
AF - atrial flutter
AFib - atrial fibrillation
ATPase - adenosine triphosphatase
A-V - arteriovenous
AVB - atrioventricular block
AV node - atrioventricular node
AVNRT - atrioventricular node reentrant tachycardia
AVRT - atrioventricular reentrant tachycardia
BAT - brown adipose tissue
BNP - B-type natriuretic peptide
BPM - beats per minute
°C - degree Celsius
Ca^{2+} - calcium
CHF - congestive heart failure
CK - creatine kinase
CK-MB - creatine kinase myocardial type
CK-MM - creatine kinase skeletal muscle type
cm - centimeter
CRP - C-reactive protein
CW - continuous wave
D2 - type 2 iodothyronine 5′- deiodinase
2D - two dimensional
dB - decibel
DNA - deoxyribonucleic acid
ECG - electrocardiography
ECLIA - electrochemiluminescence immunoassay
EDRF - endothelial derived relaxation factor
EDTA - ethylenediaminetetraacetic acid

EF - ejection fraction
EKG - electrocardiography
EMD - electromechanical delay
Eu - euthyroid
FSH - follicle stimulating hormone
F - fluorine
° F - degree Fahrenheit
fT3 - free triiodothyronine
fT4 - free thyroxine
GI - gastrointestinal
GLUT 2 - glucose transporter type 2
GnRH - gonadotropin releasing hormone
hCG - human chorionic gonadotropin
hPA - hectopascal
Hyper - hyperthyroidism
Hypo - hypothyroidism
Hz - hertz
Ibs - pounds
ICD - Implantable Cardioverter Defibrillator
IGF-I - insulin like growth factor I
IRP - International Reference Preparation
IU/ml - international unit/milliliter
K^+ - potassium
KCNQ1 - potassium voltage-gated channel subfamily Q member 1
kg - kilogram
LA - left atrium or left arm
LBBB - left bundle branch block
LDL - low density lipoprotein
LH - luteinizing hormone
Li - lithium
LL - left leg
LQTS - long QT syndrome
L-thyroxine - levothyroxine
LV - left ventricular
LVET - left ventricular ejection time
LVH - left ventricular hypertrophy
m - mini
mg - milligram
mm - millimeter
MCT8 - monocarboxylate transporter 8
MCT 10 - monocarboxylate transporter 10

MHz - megahertz
MI - myocardial infarct
min - minutes
mL - milliliters
M-mode - motion mode
mm/s - millimetrs per second
MRN - medical record number
mRNA - messenger ribonucleic acid
ms - millisecond
µIU/mL - micro-international units per milliliter
Na^+ - sodium
NBE - National Board of Electrocardiography
ng/ml - nanogram per milliliter
NH4+ - ammonium
NSVT - nonsustained ventricular tachycardia
OATP1C1 - organic anion transporting polypeptide 1C1
PEP - pre-ejection period
PEP/LVET - pre-ejection period/left ventricular ejection time ratio
PLN - phospholamban
PW - pulsed wave
QTc - corrected QT interval
QTd - QT interval dispersion
RA - right arm
RBBB - right bundle branch block
RL - right leg
RNA - ribonucleic acid
ROSC - return of spontanous circulation
SA node - sinoatrial node
SERCA - sarco-endoplasmic reticulum calcium
SNS - sympathetic nervous system
Sps - samples per seconds
SPSS - Statistical Package for the Social Sciences
SVT - supraventricular tachycardia
T3 - triiodothyronine
T4 - thyroxine
TCA - tricyclic antidepressant
TDE - tissue Doppler echocardiography
TH - thyroid hormone
THs - thyroid hormones
TPA - tripropylamine
TR - thyroid hormones receptor

TRE - thyroid hormone response element
TREs - thyroid hormone response elements
TRH - thyrotropin releasing hormone
TSH - thyroid stimulating hormone
UCP1 - uncoupling protein 1
V - voltage
V1-V6 - precordial leads in EKG
VF - ventricular fibrillation
VLDL - very-low-density lipoprotein
VT - ventricular tachycardia
WHO - World Health Organization

Part of the data was used in the article:

"Prevalence of cardiac arrhythmias in hypothyroid and euthyroid patients"

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The article has been accepted for publication in Hormone and Metabolic Research journal.

1. INTRODUCTION

1.1. THE ACTIONS OF THYROID HORMONES

The thyroid gland is the body's largest single organ specialized for endocrine hormone production. Its function is to secrete an appropriate amount of the thyroid hormones, primarily thyroxine (T4), and a lesser quantity of triiodothyronine (T3), which arises mainly from the subsequent extrathyroidal deiodination of T4. In target tissues, T3 interacts with nuclear T3 receptors that are, in turn, bound to special nucleotide sequences in the promoter regions of genes that are positively or negatively regulated by thyroid hormone. Thyroid hormones (THs) are required for the normal function of nearly all tissues, with major effects on oxygen consumption and metabolic rate. Among their life-sustaining actions, the thyroid hormones promote normal fetal and childhood growth and central nervous system development, regulate heart rate and myocardial contraction and relaxation, affect gastrointestinal motility and renal water clearance, and modulate the body's energy expenditure, heat generation, weight, and lipid metabolism [1].

1.2. THE THYROID HORMONE RECEPTORS AND MECHANISM OF ACTION

The thyroid hormones exert their actions through two general mechanisms:

- Genomic actions effected through T3 interactions with its nuclear receptors, regulating gene activity.
- Nongenomic actions mediated by T3 and T4 interactions with certain enzymes (e.g. calcium ATPase, adenylate cyclase, monomeric pyruvate kinase), glucose transporters, and mitochondrial proteins.

Thyroid hormones, that are unbound in plasma, are transported intracellularly, by either specific carrier including monocarboxylate transporter 8 (MCT8), monocarboxylate transporter 10 (MCT 10) and organic anion transporting polypeptide (OATP1C1). OATP1C1 is expressed predominantly in brain capillaries and the choroid plexus, and transporters T4 preferentially, while MCT 8 and MCT 10 are expressed in many tissues and transport both T4 and T3. Thyroid hormones are transported through the cell membrane into the cytoplasm, and subsequently into the nucleus, where T3 binds to its specific receptor [1].

There are two thyroid hormones receptor (TR) in human: TR-α and TR-β. The concentration of these receptors in tissue varies among tissues and with their stage of development. The brain contains predominantly TR-α, the liver mostly TR-β, and cardiac muscle contains both. Each of these receptors have a carboxyl terminal ligand-binding domain and a centrally located DNA-binding domain with two cysteine zinc fingers that facilitate their specific attachment to thyroid hormone response elements (TREs) in the promoters of target genes and regulate their transcription. The thyroid hormones receptors bind to thyroid hormones elements, which are typically paired, specific oligonucleotide sequences. TREs are generally located upstream of the transcription start site for the coding regions of thyroid hormone-responsive genes. In positively regulated genes, unbound TRs

interact with corepressors to repress basal transcription by recruiting histone deacetylases that alert the nearby chromatin structure. When thyroid hormones receptors are bound by triiodothyronine, these corepressor complexes are released, and the T3-bound TRs associate with coactivator complexes that promote local histone acetylation; they also associate with another protein complex (vitamin D receptor-interacting protein/TR-associated proteins) that recruits RNA polymerase II and start gene transcription. Some genes are negatively regulated by T3-bound TRs, such as pre-pro-TRH and TSH-α and β subunit genes, but the molecular mechanisms involved are currently less well understood [1]. Thyroid hormone's actions to alter expression levels of specific mRNAs and their translated proteins generate a constellation of specific tissue responses.

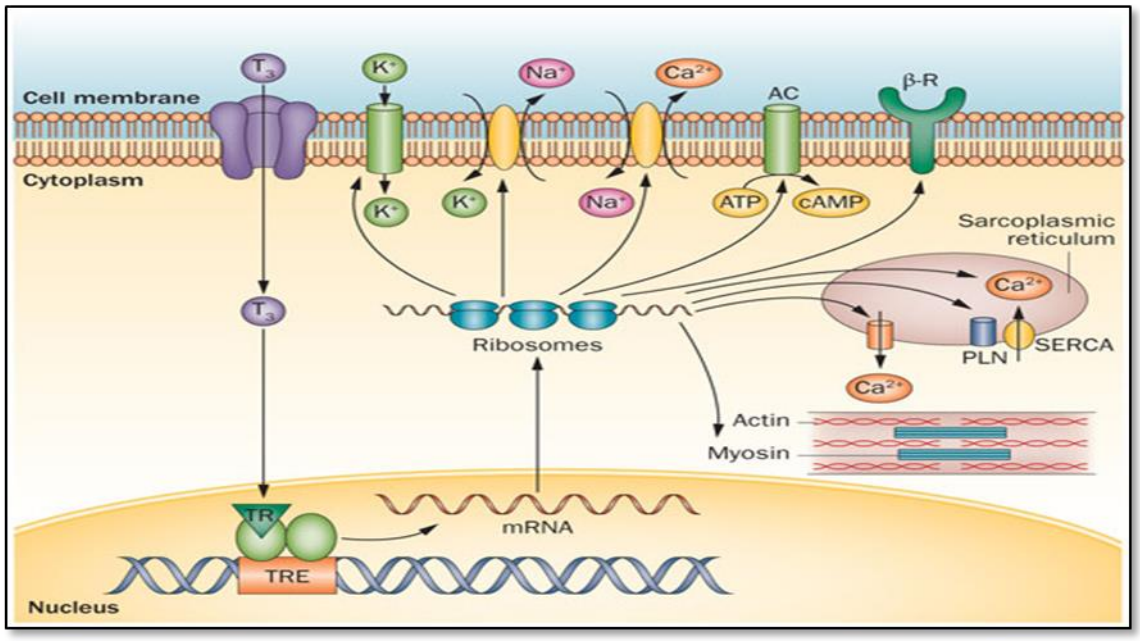

FIGURE 1 - Direct effects of T3 on the cardiomyocyte. Meuwese C, Dekkers O, Stenvinkel P, et al. Nonthyroidal illness and the cardiorenal syndrome. *Nature reviews: Nephrology*, 2013; 599-609 (modified) [2].

Binding of T_3 to thyroid hormone receptors in the nucleus of the cardiomyocyte activates thyroid hormone response elements leading to the transcription of genes encoding myosin-α, SERCA and β-R, increased expression of voltage-gated K^+ channels, Na^+/K^+ ATPase and the Na^+/Ca^{2+} exchanger, and downregulation of myosin-β, AC and PLN.
Abbreviations: AC, adenylyl cyclase; β-R, adrenergic β-1 receptor; PLN, phospholamban; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase; T_3, triiodothyronine; TR, thyroid hormone receptor; TRE, thyroid hormone response element.

1.3. PHYSIOLOGIC EFFECTS OF THYROID HORMONES

Thyroid hormones play critical roles in differentiation, growth, and metabolism. Indeed, thyroid hormones are required for the normal function of nearly all tissues. The transcriptional effects of triiodothyronine characteristically demonstrate a lag time of hours to days to achieve full effect. These genomic actions have several effects, including:

A) Vital effects:

- Tissue growth
- Brain maturation
- Increased calorigenesis
- Increased oxygen consumption

B) Specific effects on tissue:

- Heart
- Liver
- Kidneys
- Skeletal muscle
- Skin

TABLE 1 - Physiologic effects of thyroid hormones.

Target Tissue	Effect	Mechanism
Heart	Chronotropic	Increase number and affinity of β-adrenergic receptors
	Inotropic	Enhance responses to circulating catecholamines Increase proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulate lipolysis
Muscle	Catabolic	Increase protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increase rate of carbohydrate absorption
Lipoprotein	Metabolic	Stimulate formation of LDL receptors
Other	Calorigenic	Stimulate oxygen consumption by metabolically active tissues (exceptions: adult brain, testes, uterus, lymph nodes, spleen, anterior pituitary) Increase metabolic rate

1.3.1. EFFECTS ON FETAL DEVELOPMENT

Iodine concentration by thyroid tissue and pituitary thyroid stimulating hormone (TSH) both appear in the human fetus at about 11 weeks' gestation. Because of the high placental content of type 3, 5-deiodinase, most maternal triiodothyronine and thyroxine are inactivated, and very little free hormone reaches the fetal circulation. However, this small amount of free hormone from the mother is very important for early fetal brain development. After 15 to 18 weeks of gestation, the fetus is largely dependent on its own thyroid secretion. Although some fetal growth occurs in the absence of fetal thyroid hormone secretion, brain development and skeletal maturation are markedly impaired if congenital hypothyroidism is undiagnosed and thyroid hormone therapy is not begun promptly after birth [3, 4, 5]. Studies in hypothyroid neonatal rats have shown that absence of thyroid hormones cause diminished axonal growth and dendritic arborization in the cerebral cortex, visual and auditory cortex, hippocampus, and cerebellum [6, 7]. The developmental delays in the rat brain can be reversed if thyroid hormones are administered within 2 weeks after birth [8, 9]. These findings support the clinical observations that early T4 treatment of congenital hypothyroidism prevents intellectual impairment in humans and is the major impetus for neonatal screening for congenital hypothyroidism.

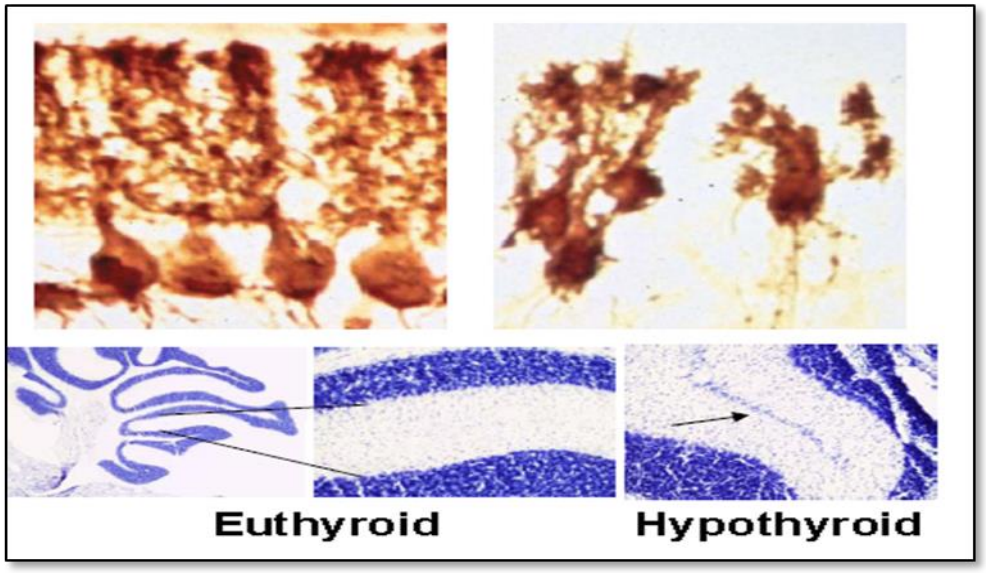

FIGURE 2 - Postnatal morphological changes in the rodent cerebellum after neonatal hypothyroidism. Bernal J. Thyroid hormones in brain development and function. *Nat Clin Pract Endocrinol Metab*, 2007; 3:249-259 (modified) [10].

Upper panel: Purkinje cells in a normal (left) and hypothyroid rat (right). Lower panel: persistence of the external granular layer (arrow) in a hypothyroid mouse cerebellum.

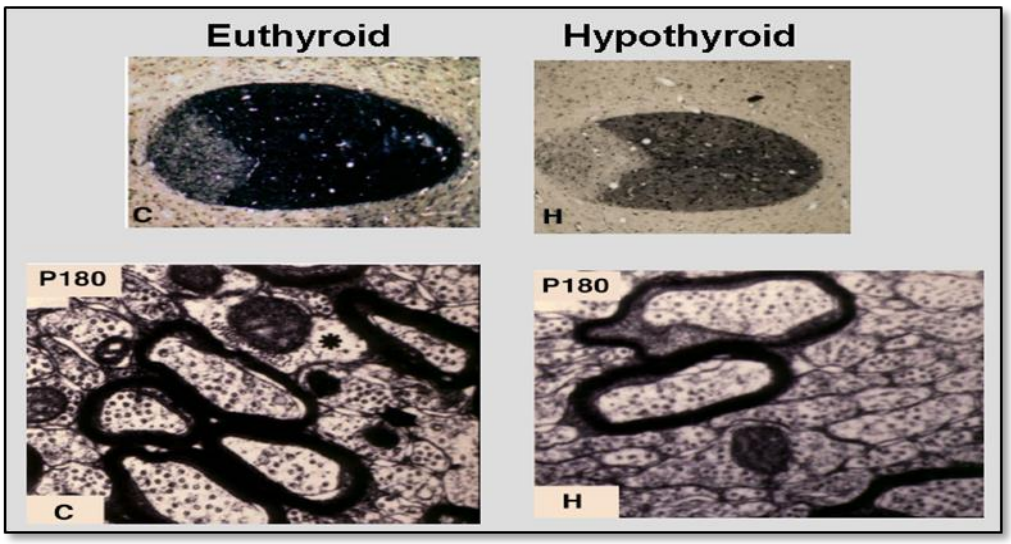

FIGURE 3 - Myelination in the anterior commissure of euthyroid and hypothyroid rats. Bernal J. Thyroid hormones in brain development and function. *Nat Clin Pract Endocrinol Metab*, 2007; 3:249-259 (modified) [10].

Upper panels: transversal section of the anterior commissure stained for myelin. The lower panels: electromicroscopy analysis. The number of myelinated axons is reduced in the hypothyroid rats

1.3.2. EFFECTS ON OXYGEN CONSUMPTION, HEAT PRODUCTION AND FREE RADICAL FORMATION

Triiodothyronine increases oxygen consumption and heat production in part by stimulation of Na^+-K^+ ATPase in all tissues except the brain, spleen and testis. This contributes to the increased basal metabolic rate (total somatic oxygen consumption at rest) and the increase sensitivity to heat in hyperthyroidism and decrease sensitivity to heat in hypothyroidism. Thyroid hormones stimulate mitochondria, augmenting the cell's oxidative capacity. They also induce changes in the mitochondrial inner membrane protein and lipid composition that increase oxidative metabolism by both genomic and nongenomic effects. The reduced efficiency of oxidative metabolism caused by thyroid hormone is also reflected in the increased futile cycling of intermediary carbohydrate metabolites [1].

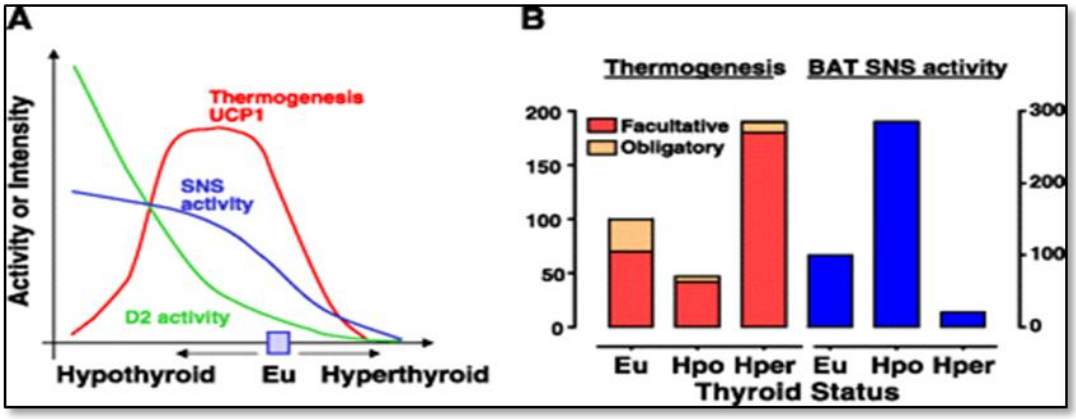

FIGURE 4 - Relationship between brown adipose tissue facultative thermogenesis and obligatory thermogenesis, sympathetic BAT stimulation and type II iodothyronine 5′-deiodinase activity as a function of thyroid status in rodents acclimated at room temperature. Silva J. Thermogenic mechanisms and their hormonal regulation. *Physiol Reviews*, 2006; 86: 435-464 (modified) [11].

A: BAT thermogenesis and UCP1 (red line), SNS activity (blue line), and D2 activity (green line) expressed as continued function of hypothyroid and hyperthyroid state departing from the euthyroid condition **B:** obligatory thermogenesis and BAT facultative thermogenesis (left axis) and BAT SNS activity (right axis) in the euthyroid status compared with hypothyroidism and hyperthyroidism. **Abbreviations**: BAT-brown adipose tissue, D2-5′-deiodinase, Eu-euthyroid, Hper-hyper, Hpo-hypo SNS-sympathetic nervous system, UCP1- uncoupling protein 1

1.3.3. EFFECTS ON THE FAT TISSUE AND CARBOHYDRATE METABOLISM

Hyperthyroidism increases hepatic gluconeogenesis and glycogenolysis, as well as intestinal glucose absorption, and they may also be thyroid hormone-mediated decreases in insulin sensitivity. Thus, hyperthyroidism can worsen glycemic control in patients with diabetes mellitus. On the other hand, reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation, gluconeogenesis, diminished hepatic glucose output and reduced disposal of glucose are hallmarks of hypothyroidism. In overt or subclinical hypothyroidism, insulin resistance leads to glucose-stimulated insulin secretion. In subclinical hypothyroidism, diminished rate of insulin stimulated glucose transport rate caused by perturbed expression of glucose transporter type 2 gene (GLUT 2) translocation may lead to insulin resistance. Cholesterol synthesis and degradation are both increased by thyroid hormones. Lipolysis is increased, releasing fatty acids and glycerol into circulating plasma. Thyroid hormones also play important roles in the development and function of brown and white adipose tissue. Thyroid hormones can induce white adipose tissue differentiation from preadipocytes in young rats [12]. Triiodothyronine not only induces intracellular lipid accumulation and various adipocyte-specific markers such as malic enzyme and glycerophosphate dehydrogenase, but also stimulates adipocyte cell proliferation and fat cell cluster formation [12, 13]. Several human studies have shown that chronic hypothyroidism or hyperthyroidism, as well as acute T3 treatment did not affect serum leptin levels [14, 15]. However, one study showed that hypothyroid patients had increased leptin levels, but the increase correlated with adiposity [16]. Another study showed that hyperthyroid patients treated with thiamazole increased their leptin level [17].

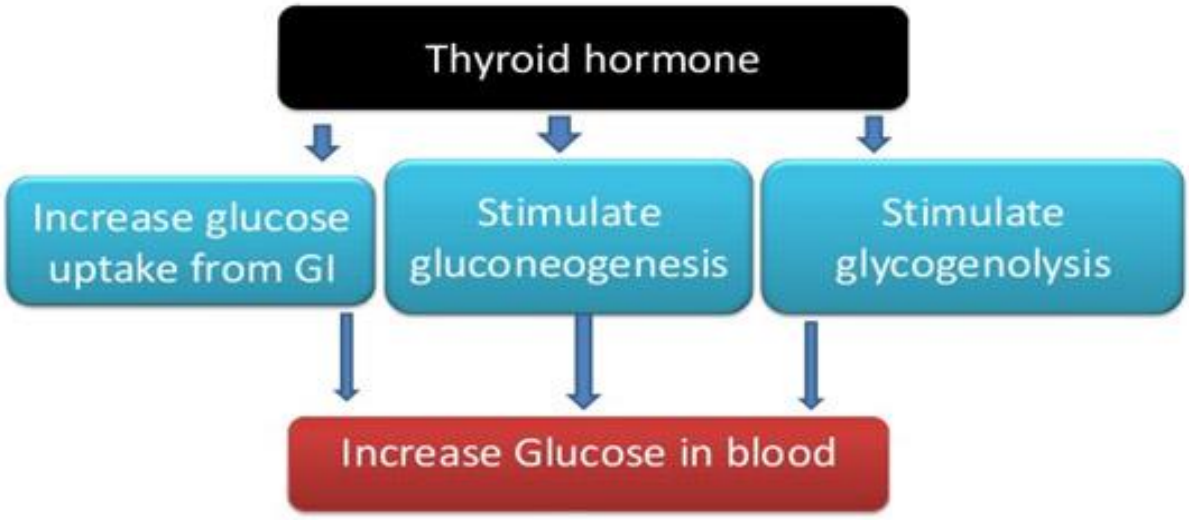

FIGURE 5 - Effects of thyroid hormones on carbohydrate metabolism. Sinha R, Singh B, Yen P. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. *Endocrinol Metab*. 2014; 25:538-545 (modified) [18].

1.3.4. EFFECTS ON THE LIVER

Thyroid hormones have multiple effects on liver function including stimulation of enzymes regulating lipogenesis and lipolysis as well as oxidative processes [19, 20]. It has been well known for many years that hypothyroidism is associated with hypercholesterolemia with elevated serum intermediate and low-density lipoprotein (LDL) cholesterol concentrations [21]. The major mechanism for these effects maybe lower cholesterol clearance resulting from decreased LDL receptors. Furthermore, the genotype of the LDL receptor gene may influence the elevation of serum LDL cholesterol concentrations in hypothyroid patients and their response to thyroxine treatment [22]. An additional mechanism may be decreased hepatic lipase activity in hypothyroidism which decreases conversion of intermediate-density lipoproteins to LDL and high-density lipoprotein (HDL) metabolism [23, 24]. Thyroid hormones also have been shown to regulate the expression of several important proteins and enzymes involved in cholesterol metabolism and synthesis such as the LDL receptor, cholesterol ester hydrolase, and cholesterol acyltransferase [25, 26].

1.3.5. EFFECTS ON THE CARDIOVASCULAR SYSTEM

Thyroid hormones lower systemic vascular resistance, increase blood volume, and have inotropic and chronotropic effects on cardiac function. The combination of these effects on both, the circulation and the heart itself, results in increased cardiac output. Hyperthyroid patients have a high output circulation state, whereas hypothyroid patients have low cardiac output, decreased stroke volume, decreased vascular volume, and increased systemic vascular resistance [27]. These changes in cardiac function ultimately depend on the regulation of target genes within the heart and indirect effects due to hemodynamic changes.

Thyroid hormones increase expression of the more rapidly contractile isoforms of myosin heavy chain, the α isoforms, which contributes to enhanced systolic function. In myocardium, T3 also alters expression of different isoforms of the Na^+/K^+- ATPase genes, increases expression of β-adrenergic receptors, and decreases the concentration of the inhibitory G protein Gi α. The rate of diastolic relaxation of the heart is related to intracellular Ca^{2+} concentration and sarcoplasmic reticulum Ca^{2+}-ATPase activity. The ATPase is an ion pump that removes calcium from the cytosol and stores in the sarcoplasmic reticulum during diastole. This decrease in the intracellular Ca^{2+} generated during systole then leads to muscle relaxation. Hypothyroid rats had decreased level of Ca^{2+}-ATPase mRNA that could be markedly stimulated by T3 administration [28]. T3 also has been shown to regulate expression of several ion channels in heart such as the voltage-gated potassium channel, Na^+/K^+- ATPase, and the hyperpolarization activated cyclic nucleotide-gated channel [29, 30]. Additionally, thyroid hormones can regulate β-adrenergic receptor number in the heart and may thereby enhance sensitivity to catecholamines [31]. Finally, a novel and potentially exciting therapeutic use of T3 as an inotropic agent has been in cardiac surgery [32]. Novitsky showed improved cardiac function and hemodynamics when brain-dead organ donors were pretreated with T3 postoperatively [32]. A small group of patients that underwent cardiac bypass surgery and were treated with postoperatively with T3 also showed some benefit [33]. However, a large randomized study showed that although T3

increased cardiac output and decreased systemic vascular resistance in patients who underwent coronary-artery bypass surgery, there was no improvement in outcome or changes in postoperative therapy [34].

T3 also increases the rates of both depolarization and repolarization of the sinoatrial (SA) node, increasing heart rate. Consequently, thyroid hormones have positive inotropic and chronotropic effects on the heart, which along with the heightened adrenergic sensitivity, accounts for the increased heart rate and contractility in hyperthyroidism and the reverse in hypothyroidism.

Thyroid hormones also lower peripheral vascular resistance, and increase intravascular volume, which contributes further to the increase in cardiac output associated with thyroid hormone action [3].

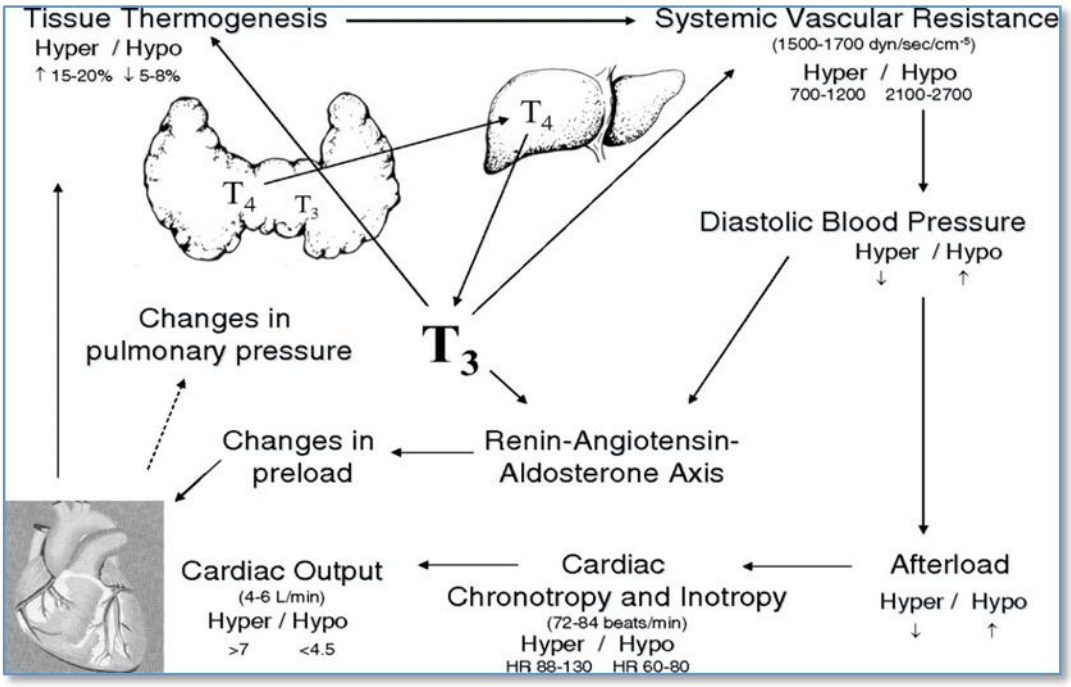

FIGURE 6. **Effects of thyroid hormone on cardiovascular hemodynamics.** Klein I, Danzi S. Cardiovascular Involvement in General Medical Conditions, *Circulation,* 2007; 15:1725-1735 (modified) [35].

T_3 affects tissue thermogenesis, systemic vascular resistance, blood volume, cardiac contractility, heart rate, and cardiac output as indicated by the arrows. **Abbreviations**: Hyper- hyperthyroidism; hypo- hypothyroidism

1.3.6. EFFECTS ON THE SKELETAL SYSTEM

Thyroid hormones are critical for normal bone growth and development. In children, hypothyroidism can cause short structure and delayed closure of the epiphyses. Thyroid hormones stimulate bone turnover, increasing bone resorption and, to a lesser degree, bone formation. Thyroid hormones may act on bone via stimulation of growth hormone (GH) and insulin-like growth factor I (IGF-I) or by direct effects on target genes. Biochemical studies have shown that thyroid hormones can affect the expression of various bone markers in serum, reflecting changes in both bone formation and resorption [36, 37, 38]. There is enhanced calcification and bone formation coupled to increased bone resorption in hyperthyroid patients [37, 39]. Additionally, the time interval between formation and subsequent mineralization of osteoid is shortened. The net effect on these bone cells is bone resorption and loss of trabecular bone thickness in hyperthyroidism. There also is marked increase in porosity and decreased cortical thickness in cortical bone in hyperthyroid patients [40, 41]. These effects can lead to osteoporosis and increased fractures. Little is known about direct thyroid hormones effects on osteoclasts. Recently, thyroid receptor protein was detected in a human osteoclastoma and in human bone samples by immunostaining, suggesting that TH might have direct effects on osteoclasts. However, two groups have used a bone slice resorption assay to show that functionally isolated osteoclasts were unable to respond directly to T3 by increasing bone resorption, and could only do so if other bone cells were present [42, 43]. These results would suggest that thyroid hormones may not have a direct effect on bone resorption but may mediate its effects via paracrine factors secreted by osteoblast cells.

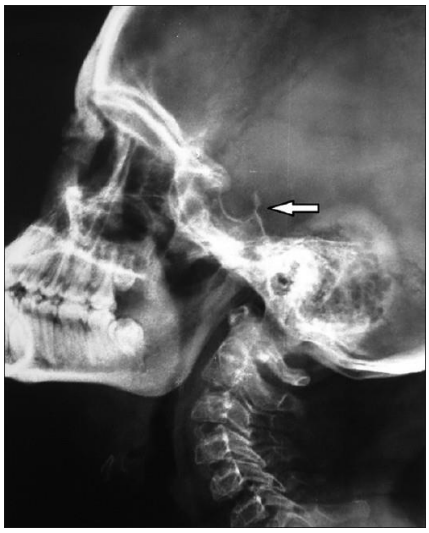

Figure A. X-ray skull: enlarged sella, hypoplastic maxillary and frontal sinuses

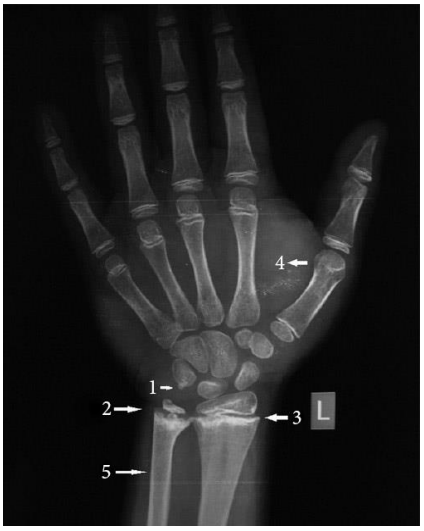

Figure B. X-ray wrist showing bone age of 10 years (chronological age 24)
1. Epiphysis of pisiform just appearing
2. Irregular ossification of growth plate
3. Sclerotic band at radial metaphysis
4. Soft tissue thickening
5. Pencil thin cortex

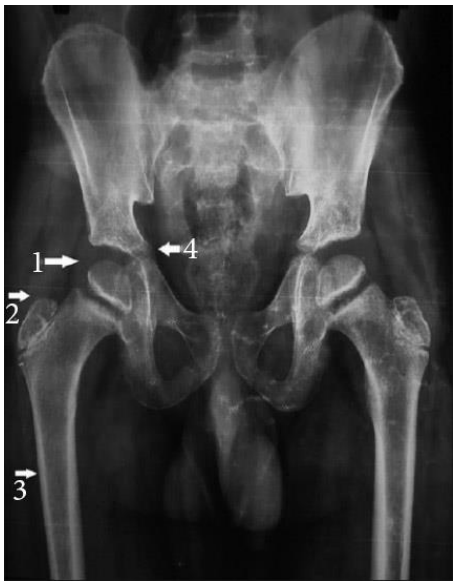

Figure C: X-ray pelvis 1. Unfused vertebral head epiphysis 2. Unfused apophysis 3. Pencil thin cortex.
4. Persistent tri radiate cartilage

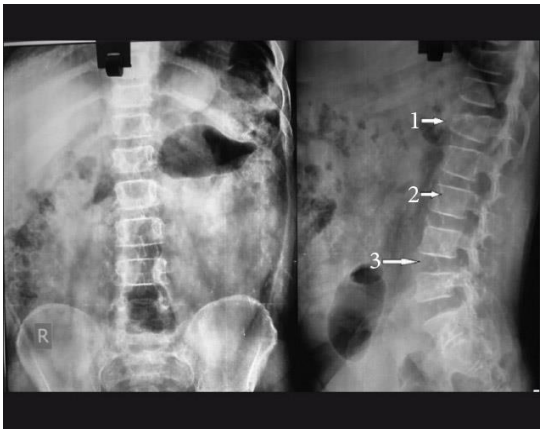

Figure D: X-ray spine 1. Bullet shaped L1 vertebra. 2. Osteoporosis 3. Increased inter vertebral spaces

FIGURE 7 - Radiological manifestations of juvenile hypothyroidism. Patidar P, Philip R, Toms A, et al. *Thyroid research and practice*, 2012: 102-104 (modified) [44].

1.3.7. EFFECTS ON PULMONARY AND GASTROINTESTINAL SYSTEM

Thyroid hormones maintain ventilator responses to hypoxia and hypercapnia in the brain stem respiratory center. Consequently, in patients with severe hypothyroidism, hypoventilation can occur. Thyroid hormone also regulates respiratory muscle functions, and they can be weakened in hypothyroidism, leading to a sense of breathlessness.

Thyroid hormones promote gut motility, which can result in increased motility and hyperdefecation (increased frequency of formed bowel movements) in hyperthyroidism. Slowed bowel transit and constipation occur in hypothyroidism.

1.3.8. EFFECTS ON THE ENDOCRINE SYSTEM

In hypothyroid children, impaired growth hormone release slows longitudinal growth. Hypothyroidism can cause delayed puberty by impairing gonadotropin-releasing hormone (GnRH) and gonadotropin secretion. Conversely, primary hypothyroidism can also cause precocious puberty. Perhaps as an effect of very high TSH levels on gonadotropin receptors. In adults, hypothyroidism causes hyperprolactinemia in a minority of affected women. Menorrhagia and anovulation are common in hypothyroid women, the latter resulting in infertility. The responsiveness of the hypothalamic-pituitary-adrenal axis to stress is blunted in hypothyroid patients. A slowing of the cortisol metabolic clearance rate compensates for this in the hypothyroid state. Conversely, restoration of euthyroidism can rarely provoke adrenal insufficiency as cortisol metabolism is accelerated in patients with diminished cortisol reserve due to concomitant disease affecting the adrenal axis. In hyperthyroidism, accelerated aromatization of androgens to estrogens and increased sex hormone-binding globulin levels contribute to the gynecomastia and elevated total testosterone levels seen in affected men. Hyperthyroidism can also impair normal GnRH and gonadotropin regulation of ovulation and menses, causing infertility and amenorrhea, respectively [3].

1.4. HYPOTHYROIDISM AND THE CARDIOVASCULAR SYSTEM

Thyroid hormone receptors are rich in the myocardium, so the heart is very sensitive to the thyroid hormones [45]. The cardiovascular signs and symptoms of thyroid disease are some of the most profound and clinically relevant findings that accompany both hypothyroidism and hyperthyroidism. Based on the understanding of the cellular mechanisms of thyroid hormone action on the heart and cardiovascular system, it is possible to explain the changes in cardiac output, cardiac contractility, blood pressure, vascular resistance, and rhythm disturbances that result from thyroid dysfunction. There are many regulatory effects of thyroid hormones, such as cardiac protein transcription and gene expression; these are effective, especially in cardiovascular endothelial and smooth muscle cells [46]. Therefore, thyroid hormone deficiency could result in significant changes in the cardiovascular system.

Hypothyroidism has various cardiovascular manifestations including:

- Impaired diastolic function
- Impaired myocardial contractility
- Decreased cardiac output and decreased heart rate
- Increased systemic vascular resistance [47]
- Endothelial dysfunction [48, 49]
- Pericardial effusion
- Heart failure [50, 51]
- Cardiac arrhythmias
- Higher prevalence of atherosclerosis

1.4.1. PATOPHYSIOLOGY

1.4.1.1. VASCULAR RESISTANCE

Thyroid hormones relax vascular smooth muscle cells, thereby reducing peripheral vascular resistance [45]. Conversely, hypothyroidism causes a decrease in the release of endothelial-derived relaxation factor (EDRF), which in turn promotes contraction of these cells thereby increasing peripheral vascular resistance. This change results in reduction in cardiac output (in part because the heart cannot increase contractility to compensate) and tissue perfusion. Tissue oxygen utilization is also decreased; thus, arteriovenous (A-V) oxygen extraction is similar to the normal subjects.

1.4.1.2. CARDIAC CONTRACTILITY

All measures of left ventricular performance are impaired in both short and long-term hypothyroidism, leading to a reduction in cardiac output. There is also a decrease in the rate of ventricular diastolic relaxation; thus, compliance and diastolic filling are impaired [52, 53, 54]. The reduced ventricular performance is probably multifactorial. Possible mechanisms include increases in afterload and changes in expression of the genes for myocardial calcium regulatory proteins [54, 55]. Several enzymes involved in regulating calcium fluxes in the heart are controlled by thyroid hormone, including the calcium-dependent adenosine triphosphatase and phospholamban [45]. Hypothyroid-dependent decreases in the expression and activity of these enzymes could potentially impaired systolic performance and diastolic relaxation. β-adrenergic receptor expression is also decreased, resulting in a blunted response to catecholamine mediated increase in inotropy.

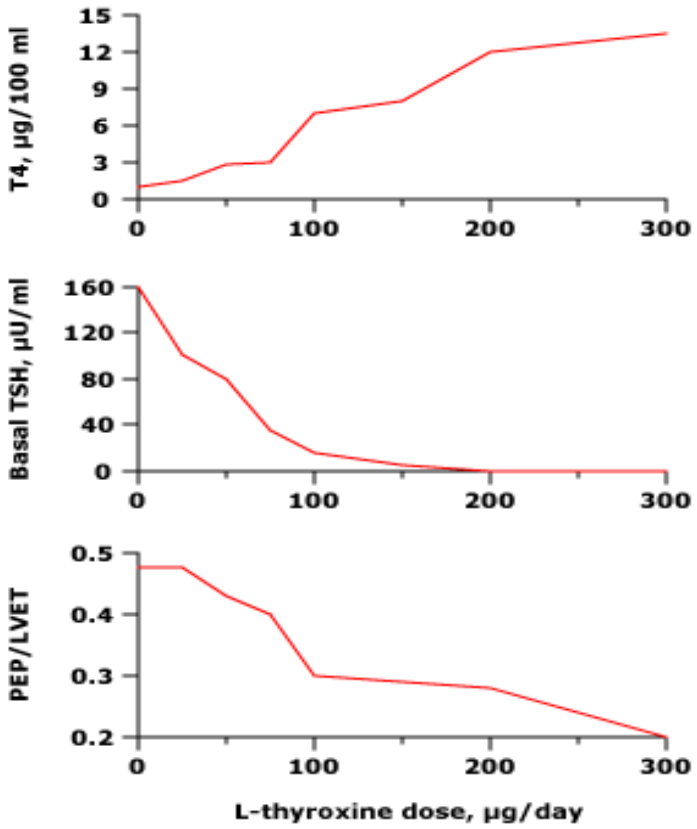

FIGURE 8 - Effect of L-thyroxine replacement in patients with hypothyroidism on serum T4, TSH, and cardiac contractility as measured by the PEP as a function of LVET.

Contractility increased (as demonstrated by a fall in PEP/LVET) in a dose-dependent fashion. Crowley W, Ridgway E, Bough E, et al. Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. *N Engl J Med* 1977; 296:301 (modified) [56].

Abbreviations: L-thyroxine: levothyroxine; LVET: left ventricular ejection time; PEP: pre-ejection period; T4: thyroxine; TSH: thyroid-stimulating hormone.

1.4.2. CLINICAL MANIFESTATION

It has been long recognized that some of the most characteristic and common signs and symptoms of thyroid disease are those that result from the effects of thyroid hormone on the heart and cardiovascular system. Those include:

- Exertional dyspnea and exercise intolerance, although these symptoms are probably due to skeletal muscle dysfunction
- Bradycardia
- Hypertension resulting from the increase in vascular resistance and the fall in endothelial-derived relaxing factor (EDRF)
- Cardiac dysfunction with poor contractility and/or dilatation
- Edema, often nonpitting
- Cardiac arrhythmias
- Pericardial effusion, which occur in approximately 25 percent of patients and may be quite large

1.4.2.1. BLOOD PRESSURE

Thyroid hormones play a role in blood pressure homeostasis. In patients who had undergone total thyroidectomy for thyroid cancer, withdrawal of thyroxine for 6 weeks results in an increase in serum norepinephrine and aldosterone concentration, and an increase in blood pressure with a greater rise in diastolic pressure (126/85 compared with 120/76 mmHg at baseline) [57]. Diastolic blood pressure varies directly with serum thyroid-stimulating hormone levels and may vary the entire spectrum of thyroid disease.

Approximately 20 to 40 percent of hypothyroid patients have hypertension, even though cardiac output is reduced. The hypertension is primary diastolic and the pulse pressure is diminished. In hypertensive hypothyroid patients, the serum levels of renin are low and there is an increased prevalence of salt sensitivity confirming the importance of the increase in systemic vascular resistance [55, 58]. Among large group of patients with hypertension, however, hypothyroidism is a contributory factor in only a small percentage.

1.4.2.2. CARDIAC DYSFUNCTION

In hypothyroidism, the upstroke of the pulse can be slow and the left ventricular apical impulse weak. In some patients on physical exam the heart sounds can be distant and the heart may be enlarged. These findings, plus dyspnea, exercise intolerance, and edema, may make it seem as if the patient has congestive heart failure. However, heart failure due solely to hypothyroidism is rare [45].

Electrocardiograms may show low voltage and nonspecific ST segment and Q wave changes. Occasionally, large pericardial effusion can occur characterized by a high protein and cholesterol content. They are rarely hemodynamically important and should be managed with thyroid hormone replacement, not by needle or surgical drainage. The latter can lead to hemodynamic worsening.

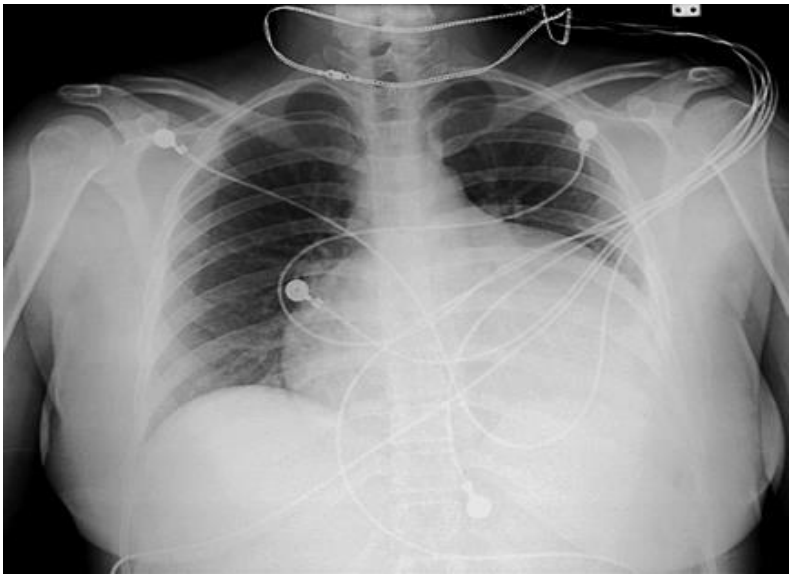

FIGURE 9 - Large pericardial effusion in severe hypothyroid woman with no underlying heart disease.

1.4.2.3. CORONARY ARTERY DISEASE

Hypothyroidism may result in accelerated atherosclerosis and coronary artery disease, presumably because of associated hypercholesterolemia, hypertension, and elevated homocysteine levels [53, 55]. Potential mechanism in addition to lipid abnormalities and diastolic hypertension include elevated concentrations of C-reactive protein (CRP) and endothelial dysfunction [59, 60]. Direct evidence of such an effect of overt hypothyroidism is lacking. However, in a study of 1149 postmenopausal women in the Netherlands, those with subclinical hypothyroidism were more likely to have a history of myocardial infarction and had a higher frequency of calcification of the aorta [68]. Thyroxine therapy may reverse the cardiovascular changes associated with hypothyroidism. In a large study of patients with hypothyroidism who were evaluated for clinical evidence of ischemic heart disease after the initiation of thyroid hormone therapy, new or worsening angina or acute myocardial infarction were rare, and more patients had improvement in angina symptoms [50]. These findings reinforce the important and potentially beneficial effects of thyroid hormone in improving the efficiency of myocardial oxygen consumption and simultaneously lowering systemic vascular resistance [50]. Whether patients with subclinical hypothyroidism should be treated is still the subject of disagreement, but from a cardiac perspective, treatment offers benefit with minimal risk.

1.4.2.4. EDEMA

Periorbital edema and nonpitting edema of the hands and feet are characteristic features of hypothyroidism, albeit rare today. Nonpitting edema is due to interstitial accumulation of glycosaminoglycans (hyaluronic acid and chondroitin sulfate), with associated extravascular water retention while plasma volume is decreased [45, 52]. Some patients have pitting edema of the feet and legs, probably secondary to an increase in albumin content of the interstitial fluid [61]. Ascites, pleural and scrotal effusions may also be present.

A) **B)**

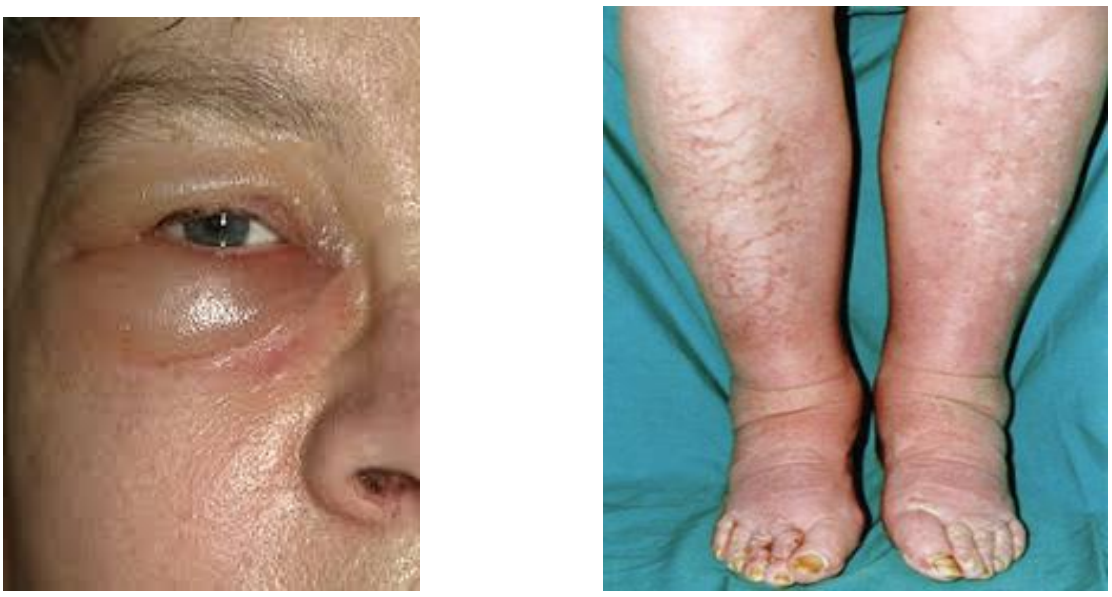

FIGURE 10 - Edema in patients with hypothyroidism A) Periorbital edema; B) Non-pitting edema of lower extremities/myxedema

1.4.3. LABORATORY TESTS

1.4.3.1. LIPIDS

Dyslipidemia is common in hypothyroidism. The usual findings are high serum total and low-density lipoprotein (LDL) cholesterol concentration. Some patients have high serum very-low-density lipoprotein (VLDL) cholesterol concentration, and a few have hypertriglyceridemia.

The spectrum and frequency of lipid abnormalities that can occur was illustrated in a report from the Mayo Clinic which evaluated 295 patients with hypothyroidism. Hypercholesterolemia was present in 56 percent of the patients, hypercholesterolemia and hypertriglyceridemia in 34 percent, and hypertriglyceridemia in 1.5 percent; only 8.5 percent had a normal lipid profile [62]. The changes in serum LDL cholesterol have been related to reduced expression of LDL receptors and decreased hepatic and biliary LDL cholesterol clearance. Another study evaluated the prevalence of hypothyroidism in patients referred for hyperlipidemia. Among 1509 consecutive patients, hypothyroidism was present in 4.2 percent, approximately twice the incidence than in the general population [63]. In view of the increased prevalence of hypercholesterolemia, especially in patients with overt hypothyroidism (TSH>20 μIU/mL), the question of optimum therapy often arises. If hypothyroidism is present, the patient should be treated for 3 to 4 months with thyroid hormone to normalized serum TSH. If the serum lipid concentrations are not then normal, specific lipid-lowering therapy may be indicated. It should be noted that hypothyroidism may predispose to the development of statin-associated myopathy and that use of statins may unmask hypothyroid myopathy.

1.4.3.2. HOMOCYSTEINE

Some patients with hypothyroidism have high serum homocysteine concentrations, which fall toward if not to normal with LT4 therapy.

1.4.3.3. CREATINE KINASE

Many hypothyroidism patients have high serum creatine kinase (CK) concentrations. The isoenzyme distribution is almost completely CK-MM, with less than 4 percent constituting CK-MB, indicating skeletal muscle, not myocardial, origin [64]. However, as many as 14 percent of patients with hypothyroidism have a raised serum concentration of CK-MB, which can be confusing in the evaluation of chest pain. The problem is obviated by measurement of serum troponin I, which is normal in hypothyroidism [65].

1.4.4. RHYTHM DISTURBANCES

In addition to slow pulse rate, hypothyroid patients may have ventricular premature beats and rarely ventricular tachycardia with a long QT interval (torsades de pointes). This can be especially problematic in patients with underlying ischemic heart disease or known ventricular arrhythmias.

EKG changes in hypothyroidism involve:

1) Bradycardia
2) Right bundle branch block (RBBB)
3) Flat or inverted T wave
4) QRS prolongation
5) QT prolongation
6) Torsades de pointes

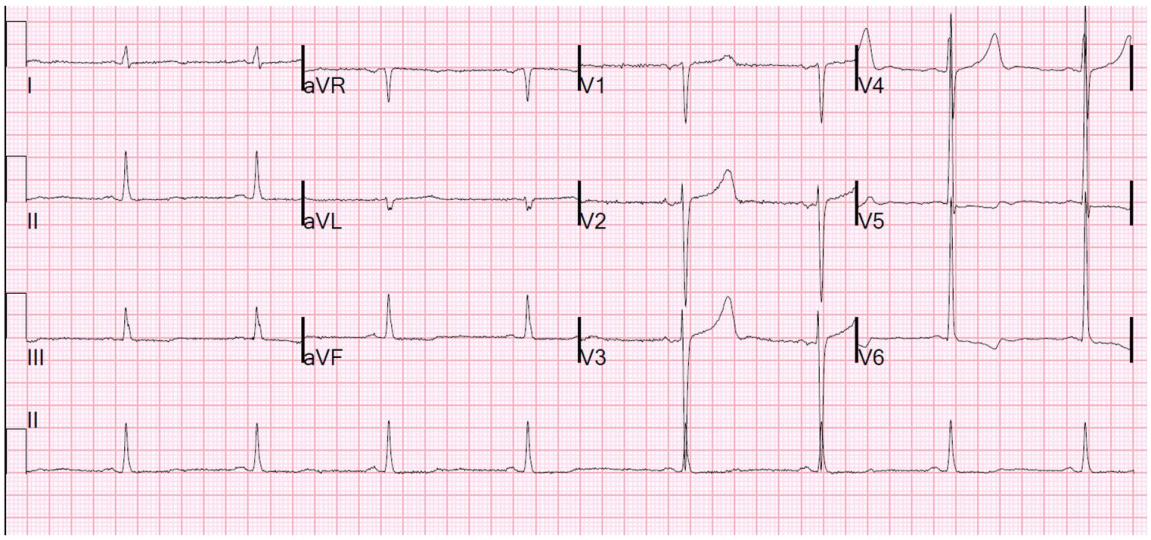

FIGURE 11 - Sinus bradycardia.

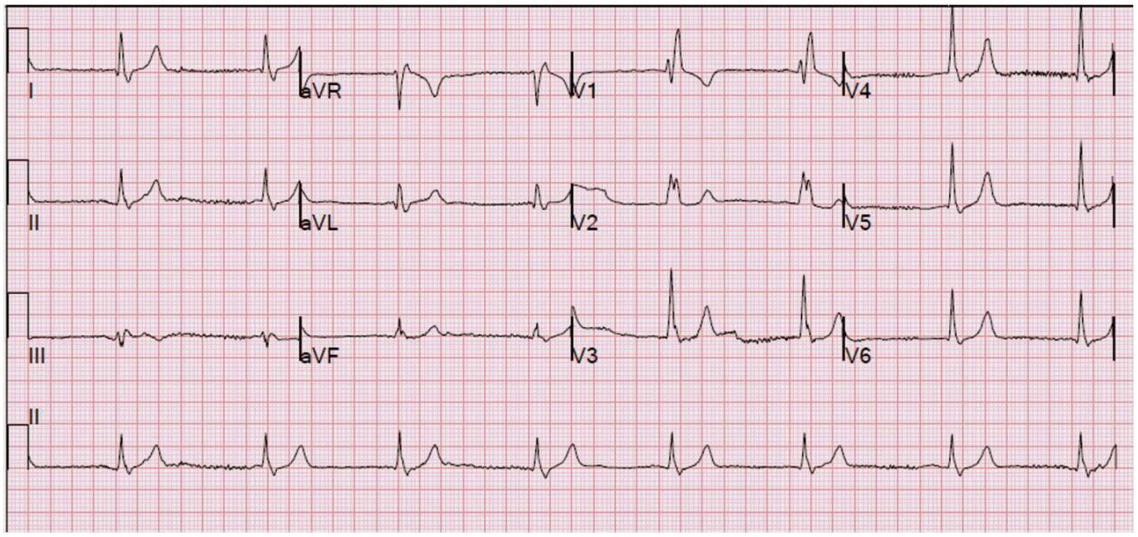

FIGURE 12 - Right bundle branch block (RBBB).

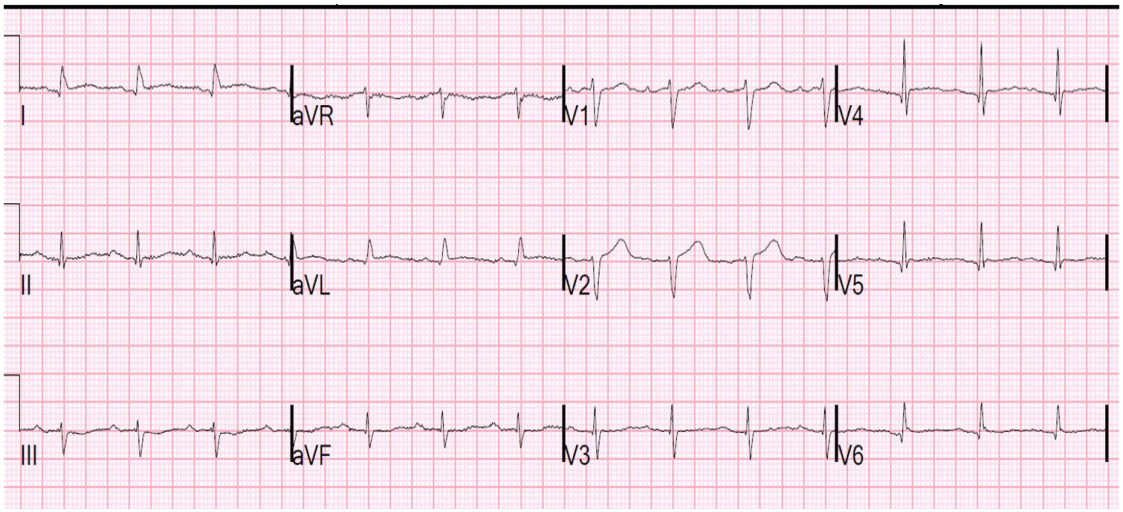

FIGURE 13 - Flat T waves.

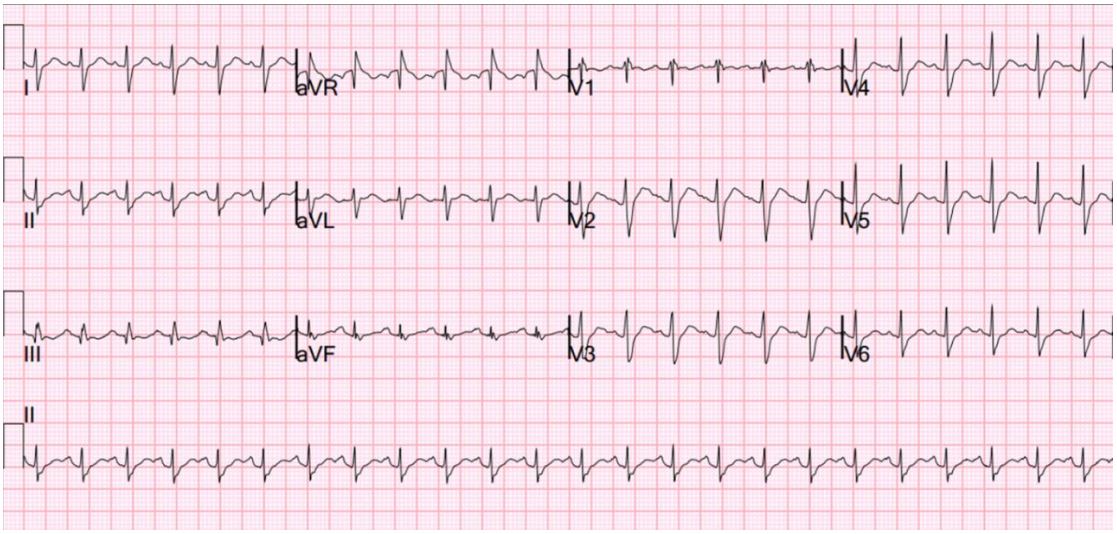

FIGURE 14 - QRS prolongation.

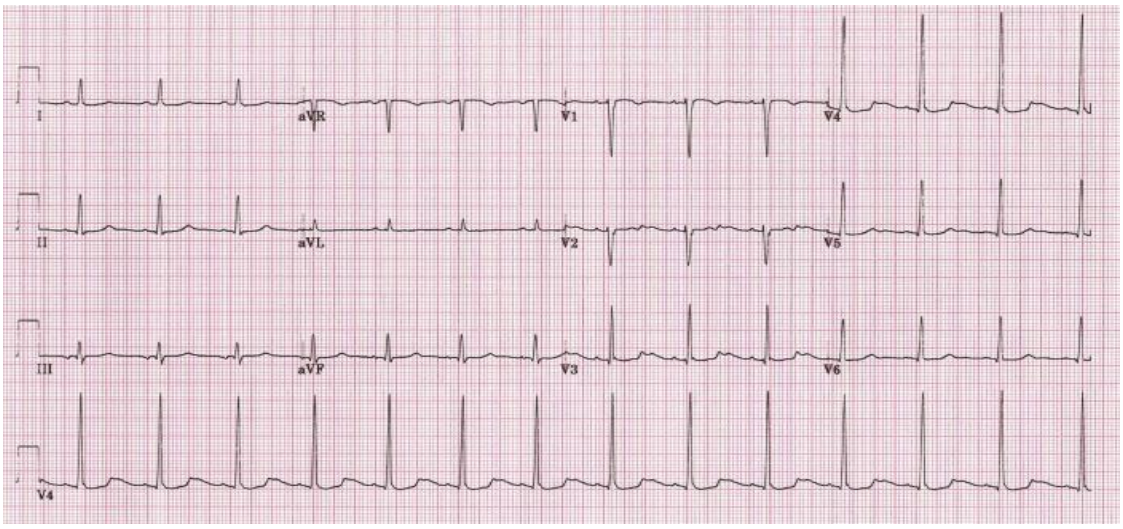

FIGURE 15 - QT prolongation.

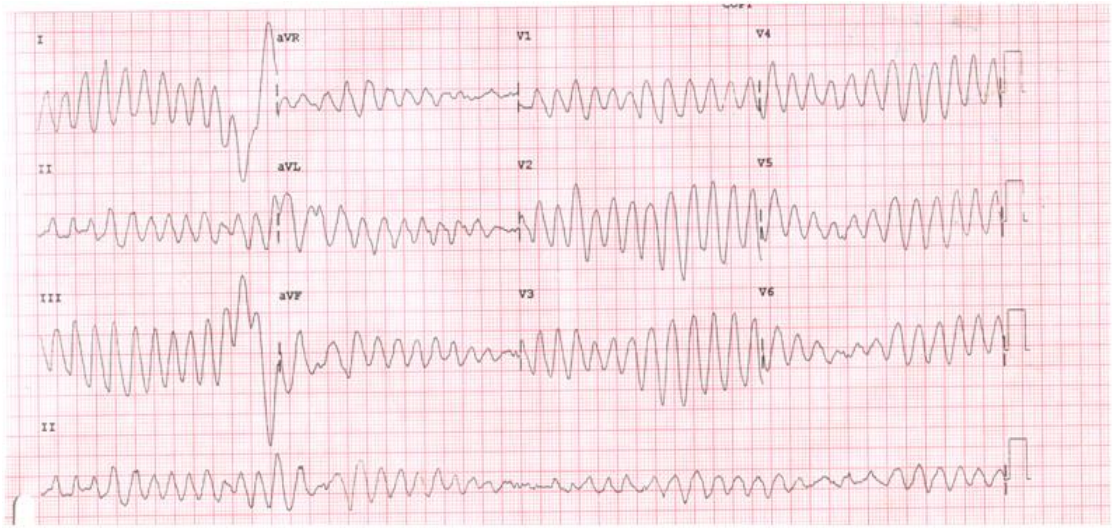

FIGURE 16 - Torsade de pointes.

2. THESIS AND AIMS OF THE STUDY

Thyroid hormones affect various functions of the heart including contractility and chronotropic functions of the heart. The association of hyperthyroidism with atrial tachyarrhythmias is well established but little is known about the association of hypothyroidism and cardiac arrhythmias. Though EKG changes in hypothyroidism, including prolongation of QT interval, QRS interval and bradycardias, are well known, still little is known about the clinical significance of these EKG changes including the incidence and prevalence of cardiac arrhythmias and the need for periodic surveillance in these patients for arrhythmias.

Increased QT has been found to be associated with an increased incidence of malignant ventricular arrhythmias and sudden death, however a few clinical observations showed that sudden death is uncommon in hypothyroidism despite the marked lengthening of the QT interval [75, 76, 77]. There were also studies which showed that QT dispersions improved after the L-thyroxine treatment in patients with primary hypothyroidism [78]. This suggests that the L-thyroxine replacement therapy may reduce malignant ventricular arrhythmia and sudden cardiac death in patients with hypothyroidism.

Patients with thyroid dysfunction are as such at increased risk for cardiovascular morbidity and mortality through an increased prevalence of ischemic heart disease and congestive heart failure (CHF), both of which predispose to the development of cardiac arrhythmias. Independent of these conditions it is unsure if hypothyroid status *per se* predisposes to cardiac arrhythmias.

2.1. THESIS OF THE STUDY

Despite these facts about cardiac arrhythmias in hypothyroid patients, very few clinical studies have addressed the prevalence of cardiac arrhythmias in hypothyroidism. This relatively large a retrospective age-, gender- and ethnicity-matched case control study was conducted to analyze differences, if any, in the prevalence of cardiac arrhythmias between hypothyroid patients and euthyroid control group. One of the aims of this study is to throw light on the prevalence of arrhythmias in hypothyroidism and detect necessitates for future large scale prospective studies to better define the risk of such ventricular arrhythmias and the effects of thyroid supplementation on this risk. Identifying the life-threatening arrhythmias in patients with hypothyroidism can help to detect disease earlier, prolong survival, and decrease overall mortality in this group of patients. These patients may need more intensive preventive care for arrhythmias than general population.

2.2. AIMS OF THE STUDY

1) Detect the prevalence of cardiac arrhythmias in patients with hypothyroidism.
2) Analyze differences in the prevalence of cardiac arrhythmias between hypothyroid patients and patients with normal thyroid function.
3) Establish clinical significance and the need for periodic surveillance for arrhythmias in hypothyroid patients.

3. PATIENTS, MATERIALS, AND METHODS

3.1. STUDY DESIGN AND PATIENTS ENROLLMENT

Approval for the study was obtained from the Albert Einstein Medical Center Ethics Committee (IRB ID: 4601 EXE). Retrospective chart analysis was performed. Demographic data including age, gender, and ethnicity were collected. Age, gender, and ethnicity matched controls were selected from the euthyroid group. Each hypothyroid patient was matched against the euthyroid subject by random allocation in chronological order of hospitalization. Data regarding specific arrhythmias were obtained from the EKG, chart documentation of known past medical history and from telemetry recordings during the index hospitalization. History of cardiac arrhythmias included:

1) Tachyarrhythmias

- atrial fibrillation (AFib)
- atrial flutter (AF)
- atrial tachycardia
- atrioventricular reentrant tachycardia (AVRT)
- atrioventricular node reentrant tachycardia (AVNRT)
- ventricular tachycardia (VT)
- nonsustained ventricular tachycardia
- ventricular fibrillation (VF)

2) Bradyarrhythmias

- sinus bradycardia
- atrioventricular block (AVB)
- junctional rhythms
- idioventricular rhythm

Left ventricular systolic and diastolic function were evaluated based on transthoracic echocardiogram result, chest x-ray, physical exam and elevated B-type natriuretic peptide (BNP) level. Patients were classified into three categories:

1. Any congestive heart failure if either systolic or diastolic function was compromised.
2. Systolic CHF if ejection fraction (EF) was below 50% (Cardiologist at Albert Einstein Medical Center, Philadelphia use criteria of EF<50% to diagnose systolic CHF).
3. Only diastolic dysfunction per Echocardiography report (based on E/A ratio).

Typical chest x-ray changes in patients with congestive heart failure included: pulmonary venous congestion, interstitial edema, pleural effusion, and cardiomegaly. Only patients who based on Framingham diagnostic criteria met two major criteria (acute pulmonary edema, cardiomegaly, hepatojugular reflex, neck vein distention, paroxysmal nocturnal dyspnea or orthopnea, rales, third heart sound gallop) or one major and two minor criteria (ankle edema, dyspnea on exertion, hepatomegaly, nocturnal cough, pleural effusion, and tachycardia >120 beats per minute) were included as congestive heart failure patients.

From 5642 patients who were admitted to the Cardiology Floor at Albert Einstein Medical Center in Philadelphia, Pennsylvania, United States of America between 1st of June 2011 and 31st of May 2012, there were 214 patients who met criteria for potential subjects for the study based on the level of thyroid stimulating hormone >10 μIU/mL followed by confirmation with low level of free thyroxine. After applying exclusion criteria described below, 152 patients were selected as a study group. 152 subjects who were euthyroid based on TSH level were age-, gender- and ethnic- matched and selected as a control group. The main reasons for admissions to Cardiology Floor were: chest pain, myocardial infarct, unstable angina, syncope, congestive heart failure exacerbation, atrial fibrillation with rapid ventricular response and cardiomyopathy.

3.1.1. SUBJECTS

Patients with TSH level >10 μIU/mL followed by confirmation with low level of circulating free thyroxine were included in the hypothyroid group and considered eligible for the subject group after applying specific cardiac exclusion criteria as listed in Table 2.

TABLE 2 - Exclusion cardiac criteria for hypothyroid group.

TABLE 2. EXCLUSION CRITERIA FOR HYPOTHYROID GROUP
1. Patients with a pacemaker implanted
2. Patients with an Implantable Cardioverter Defibrillator (ICD)
3. Patients with congenital long QT syndrome
4. Patients within 30 days post myocardial infarction (MI)
5. Patients with arrhythmias due to documented electrolyte abnormalities- hypokalemia, hyperkalemia, hypomagnesemia, hypocalcemia, hypercalcemia

All patients who were taking medications that might interfere with the accuracy of TSH measurement were also excluded from the study.

Drugs that can increase TSH include the following:

- Dopamine antagonists
- Chlorpromazine
- Haloperidol
- Iodine-containing drugs
- Amiodarone (amiodarone-induced hypothyroidism)

Drugs that can decrease TSH include the following:

- Metformin
- Dopamine
- Levodopa
- Bromocriptine
- Glucocorticoids (>0.5 mg/day dexamethasone, 100 mg/day hydrocortisone)
- Somatostatin analogs (octreotide, lanrerotide)
- Amphetamines

3.1.2. CONTROL GROUP

Subjects who were euthyroid based on physical examination and TSH level were chosen as a control group, with the TSH cut-off defined as within the lab reference range for the assay performed. Such patients were included in the euthyroid group after applying specific cardiac exclusion criteria as listed in Table 3.

TABLE 3 - Exclusion cardiac criteria for euthyroid group.

TABLE 3. EXCLUSION CRITERIA FOR EUTHYROID GROUP
Patients with a diagnosis of hypothyroidism and on levothyroxine supplementation
Patients with a pacemaker implanted
Patients with an Implantable Cardioverter Defibrillator (ICD)
Patients with congenital long QT syndrome
Patients within 30 days post myocardial infarction (MI)
Patients with arrhythmias due to documented electrolyte abnormalities- hypokalemia, hyperkalemia, hypomagnesemia, hypocalcemia, hypercalcemia

3.2. STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Platform, Stata/IC 13 for Windows 10 (version 11.0, SPSS Inc, Chicago, Ill, USA) and Microsoft Excel. Group differences were analyzed using Student t-test for parametric data and Mann-Whitney U test for nonparametric data. Group differences in the prevalence of individual cardiac arrhythmias were analyzed using Chi-square test. Continues variables were presented as mean +/- standard deviation and categorical variables were presented as the percentage. A value of $p < 0.05$ was considered statistically significant.

3.3. METHODS

3.3.1. PLASMA THYROID STIMULATING HORMONE LEVEL

Thyroid stimulating hormone stimulates the production and secretion of the metabolically active thyroid hormones, thyroxine and triiodothyronine, by interacting with a specific receptor on the thyroid cell surface. TSH is composed of two non-covalently linked subunits, designated α and β. Although the α subunit of TSH is common to luteinizing hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG), the β subunits of these glycoproteins are hormone specific and confer biological as well as immunological specificity. The synthesis and secretion of TSH is stimulated by the thyrotropin releasing hormone (TRH), the hypothalamic tripeptide, in response to low levels of circulating thyroid hormones. Elevated levels of T3 and T4 suppress the production of TSH via a classic negative feedback mechanism. Recent evidence also indicates that somatostatin and dopamine exert inhibitory control over TSH release, suggesting that the hypothalamus may provide both an inhibitory and stimulatory influence on pituitary TSH production [1].

The measurement of plasma TSH is the commonly accepted and most sensitive screening test for primary thyroid disorder, because the pituitary gland responds with great changes in its secretion, even to slight changes in the levels of free thyroid hormones. The sensitivity of its measurement in the diagnostics of tissue hormone excess is estimated to be higher than 95%, and the specificity-approximately 90%, while its daily fluctuations are very small and are of no importance for the interpretation of results [83, 84, 85].

The determination of TSH serves not only as a preliminary test in the differentiation of the thyreologic state of the population, but also plays the role of a predictive factor of the

occurrence of malignant changes within the nodules [86]. In the past, the TSH test was the only test performed in the diagnostics of thyroid function; however, it seems that for a genuine and objective assessment of the thyreologic state, the level of TSH, together with fT4 level, should be determined, which allows the identification of patients with pathology of the hypothalamo-pituitary system with respect to thyroid axis. At the same time, an abnormal TSH level makes it necessary to determine the peripheral hormone levels, and form of free thyroid hormones fT4 and fT3, which enables evaluation of the intensity of thyroid function disorders and foresee its consequences [87, 88].

The currently applied methods for the determination of TSH are characterized by a much higher sensitivity and specificity, due to the use of two monoclonal antibodies identifying two different epitopes of the TSH, which allowed the elimination of cross-reactivity. A National Academy of Clinical Biochemistry guideline specifies that sensitivity, or lower limit of detection, for TSH assays should be less than 0.02 μIU/mL (third-generation methods). This permits patients with nonthyroidal illness to be distinguished from those with primary hyperthyroidism. This is particularly important in patients hospitalized with nonthyroidal illness where TSH concentration as low as 0.02 μIU/mL may be encountered [89].

TABLE 4 - Typical TSH findings.

TSH	Free T4	Free or total T3	Probable interpretation
High	Normal	Normal	Subclinical hypothyroidism
High	Low	Low or normal	Primary hypothyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	High or normal	High or normal	Primary hyperthyroidism
Low	Low or normal	Low or normal	Non-thyroidal illness; pituitary (secondary) hypothyroidism
Normal	High	High	Thyroid hormone resistance syndrome

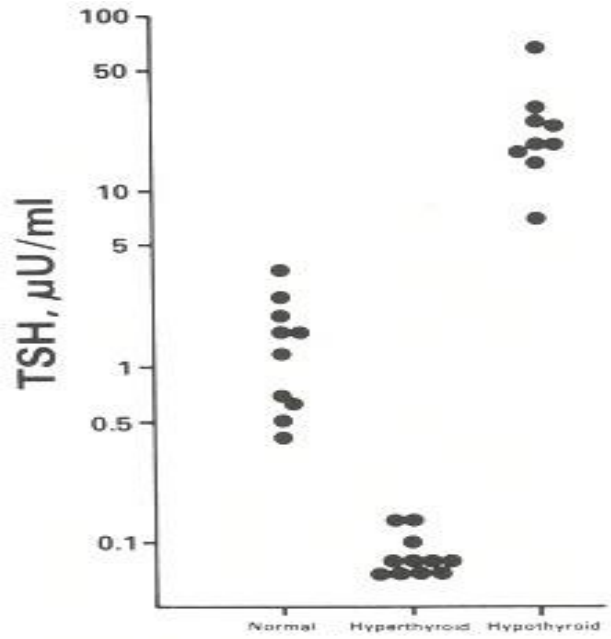

FIGURE 17 - Serum TSH in various states of thyroid function. Dunlap D. Clinical methods: The history, physical, and laboratory examinations. 3rd edition. Chapter 142 [142].

3.3.1.1. TSH TEST PROCEDURE

All patients included in the study had TSH level checked with Roche Elecsys System using Cobas E 411 analyzer provided by LabCorp Laboratory. Roche Elecsys system is intended to be an immunoassay for the quantitative determination of thyrotropin in human serum and plasma and is standardized to the World Health Organization (WHO) Second International Standard for Human TSH (IRP 80/588). It is a third-generation assay for TSH and has a functional sensitivity as low as 0.014 μIU/mL. In this study the reference TSH interval was 0.450−4.500 μIU/mL.

Only patients with TSH level >10 μIU/mL followed by confirmation with low levels of circulating thyroid hormone levels (fT4) were selected as a study group (hypothyroid group). Patients with the TSH cut-off defined as within the lab reference range for the assay performed were chosen as a control group (euthyroid group).

TEST PROCEDURE

Entire procedure took about 15-20 minutes.

1) First, the written consent for the blood work was taken from every patient and patients were informed about possible complications which included:

- Excessive bleeding
- Fainting or feeling light-headed
- Hematoma

2) The area on the arm was cleaned with an antiseptic solution

3) An elastic band was tied around the arm to increase blood flow within the vessel

4) A needle was inserted into the vein to draw blood. The blood was collected in a small tube attached to the needle (red-top tube or gel-barrier tube)

5) The tube labeled with patient's name and medical record number (MRN) was sent to the lab for analysis

6) LabCorp Laboratory measured TSH level using Roche Elecsys system with Cobas E 411 analyzer

7) All abnormal results were confirmed with fT4 test and uploaded in the computer system

TABLE 5 - TSH test characteristics.

Feature	Specification
Laboratory	LabCorp
Test name	Thyroid-stimulating Hormone (TSH)
Test Number	004250
Methodology	Electrochemiluminescence immunoassay (ECLIA)
Specimen	Serum
Volume	0.8 mL
Minimum volume	0.3 mL
Container	Red-top tube or gel-barrier tube
Collection	If a red-top tube was used, separated serum was transported to a plastic transport tube
Storage	Room temperature
Stability	Room temperature 14 days Refrigerated 14 days Frozen 14 days Freeze/thaw cycles Stable x3
Causes for rejection	Citrate plasma specimen; improper labeling

TABLE 6 - Reference interval of TSH test (units µIU/mL).

Age	Range (µIU/mL)
0 to 6 days	0.700−15.200
7 days to 3 months	0.720−11.000
> 3 months to 12 months	0.730−8.350
1 to 5 years	0.700−5.970
6 to 10 years	0.600−4.840
>10 years	0.450−4.500

3.3.1.2. ELECTROCHEMILUMINESCENCE (ECLIA)

Roche Elecsys System uses Electrochemiluminescence (ECLIA) method to measure TSH level. Based on this technology and combined with well-designed, specific and sensitive immunoassays, Elecsys delivers reliable results. ECLIA is a kind of luminescence produced during electrochemical reactions in solution. It combines the analytical advantages of chemiluminescent analysis (absence of background optical signal) with ease of reaction control by applying electrode potential. Enhanced selectivity of ECLIA analysis is reached by variation of electrode potential thus controlling groups that are oxidized/reduced at the electrode and take part in ECLIA reaction.

In electrogenerated chemiluminescence, electrochemically generated intermediates undergo a highly exergonic reaction to produce an electronically excited state that emits light. ECLIA excitation is caused by energetic electron transfer (redox) reactions of electrogenerated species. Such luminescence excitation is a form of chemiluminescence where all reactants are produced electrochemically on the electrodes. ECLIA is usually observed during the application of potential (voltage) to electrodes of electrochemical cell that contains solution of luminescent species (polycyclic aromatic hydrocarbons, metal complexes) in aprotic organic solvent (ECLIA composition) [90]. The development of ECLIA immunoassays is based on the use of a ruthenium-complex and tripropylamine (TPA). The chemiluminescence reaction for the detection of the reaction complex is initiated by applying a voltage to the sample solution resulting in a precisely controlled reaction [91].

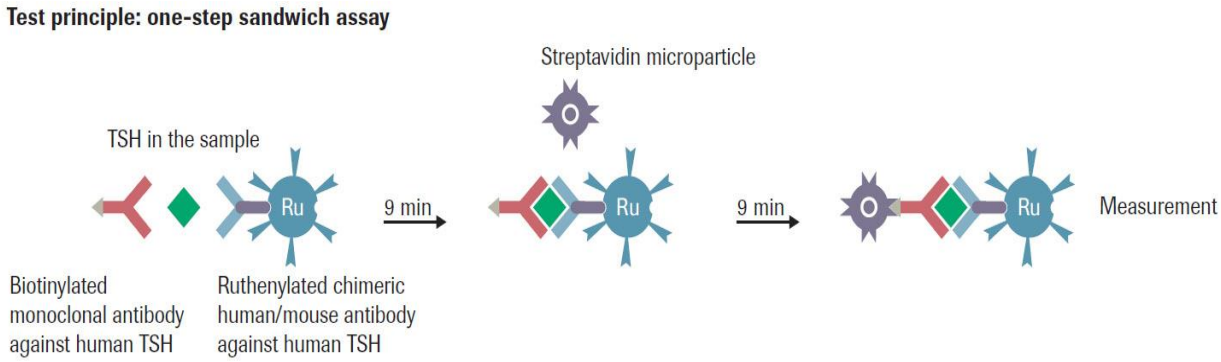

FIGURE 18 - Elecsys TSH. Electrochemiluminescence (ECLIA). Roche Diagnostics (modified).

Elecsys TSH test (ECLIA method) was done by LabCorp laboratory technician in 3 steps:

1) 1st incubation (9 minutes)

50 µL of sample, a biotinylated monoclonal TSH-specific antibody and a monoclonal TSH-specific antibody labeled with a ruthenium complex were incubated. A sandwich-complex was formed with TSH carrying a biotinylated and a ruthenylated anti-body against different epitopes on human TSH.

2) 2nd incubation (9 minutes)

After addition of streptavidin-coated microparticles the complex became bound to the solid phase via interaction of biotin and streptavidin.

3) Measurement

The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. Unbound substances were then removed. Application of a voltage to the electrode then induced chemiluminescent emission

which was measured by a photomultiplier. The signal yield was roughly proportional to the TSH concentration in the sample.

TABLE 7 - Sets used in Elecsys TSH test.

Device name	Feature	Description	Catalog number
Reagent	Elecsys TSH	200 tests	11731459
Calibrator	TSH CalSet	4x1.3 mL	04738551
Control	PreciControl Universal	2x3 mL each	11731416
Analyzer	PreciControl TSH	4x2 mL	11776479
Assay	Diluent MultiAssay	2x16 mL	03609987

TABLE 8 - Elecsys TSH test characteristics.

Feature	Specification
Testing time	18 min
Test principle	One-step sandwich assay
Detection/Operating Principle	Chemiluminescence
Solid Phase	Micro-particle
Sample type	Serum and plasma
Antibody	Monoclonal anti-TSH mouse antibody
Solid phase binding principle	Biotin and streptavidin
Analyzer Reagents	On-board Storage Bar-coded (1-D & 2-D) reagent,

	calibrator & control Cap/septum for increased reagen stability and evaporation control
Reagent, Calibrator and Control	Liquid
Calibration and Control Stability	Unopened •At 2-8°C up to the stated expiration date Opened •28 days / 4 weeks at 2-8°C
Calibration	2 point
Sample material	Serum, Li-, Na-, NH4+-heparin plasma, K3-EDTA, Na-citrate, NaF, K-oxalate plasma
Sample volume	50 µL
Detection limit	0.005 µIU/mL
Functional sensitivity	0.014 µIU/mL
Measuring range	0.005 - 100 µIU/mL
Traceability	2nd IRP WHO Reference Standard 80/558
Total imprecision (NCCLS)	cobas e 411 analyzer, E2010: 1.8 - 8.7% cobas e 601 / e 602 modules, E170: 3.2 - 7.2%
Expected values	0.27 - 4.2 µIU/mL (95th percentile)
Analyzer Sample Detection	Liquid Level Detection Clot Detection
Calibrator Matrix	Horse serum with added recombinant TSH
Analyzer Host Interface	RS232C bidirectional

3.3.2. ELECTROCARDIOGRAPHY (EKG)

All subjects underwent standard 12-lead EKG, acquired using the MAC 5500 electrocardiograph (GE Healthcare, Milian, Italy) at a paper speed of 25 mm/s and 10 mm/Mv. Patients were informed of the procedure to be performed, emphasizing that it is painless and harmless but they must lie still, breathe normally and refrain from talking. Proper skin preparation, with shaving if necessary, was required to reduce impedance and ensure adhesion of the electrode. This greatly helped to minimize the appearance of artifacts that can sometimes cause significant diagnostic errors. All recordings were performed in a controlled environment through spontaneous breathing, the subsequent 15 minutes of adjustment in the supine position. EKG interpretations were performed by certified cardiologist from Department of Cardiology at Albert Einstein Medical Center in Philadelphia, United States of America.

3.3.2.1. EKG LEADS PLACEMENT

1. Positioning patient

The standard position of the patient was used- supine with head flat or at no more than a 45-degree angle, with arms and legs free. If the patient could not lie with their head flat or at no more than 45-degrees, patient was positioned for comfort. Altered position was documented, so the physician could consider the position when interpreting the EKG.

2. Skin preparation

By protocol each area where electrodes are to be placed must be cleaned properly. Alcohol pad was used to de-fat the skin and a dry cloth or 2 by 2 gauze pad were used to gently abrade the top layer of cells of the skin. Not only does this ensure full contact of the electrode with the skin for best conduction, but also reduced noise and improved the quality of the recorded EKG. A special consideration was made for hairy chests; shaving was done only when it was necessary.

TABLE 9 - Skin preparation.

Normal	Oily	Diaphoretic
	If skin was very oily or soiled, it was washed with soap and water; dry	Briskly rub skin with dry cloth to dry
Skin was cleaned with alcohol pad and allowed to dry	Briskly rub skin with alcohol pad- allow to dry	Clean skin with alcohol pad- allow to dry
Briskly rub skin with dry 2x2 pad	Briskly rub skin with dry 2x2 pad	Briskly rub skin with dry 2x2 pad

3. Lead electrode placement

Total of 10 electrodes were used. There were four electrodes for limb leads named RA (right arm), LA (left arm), RL (right leg) and LL (left leg). There were six electrodes for chest leads named V1 through V6. EKG technician checked if electrodes adhered to the skin and laid flat against the skin. Electrodes could point in any direction as long as they maintained full contact with the skin when connected and there was no stress or pulling on the lead wires. Before performing the EKG, double check was made that the leads clips/wires were securely attached and going to the correct electrode.

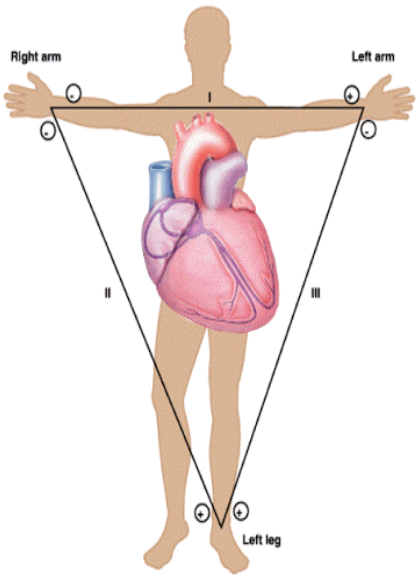

FIGURE 19 - Placement of the limb electrode. Electrocardiogram leads, Electrocar Diogram, June 2012 [135].

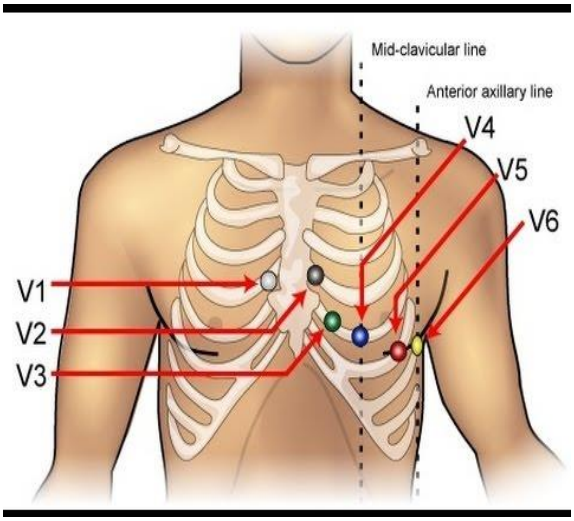

FIGURE 20 - Placement of the precordial electrodes. Clores L, ECG leads placement, *Nursing crib*, Medical laboratory and diagnostic tests, March 2014 [136].

TABLE 10 - The electrodes in a 12 lead-EKG.

Electrode name	Electrode placement
RA	On the right arm, avoiding thick muscle
LA	In the same location where RA was placed, but on the left arm
RL	On the right leg, lateral calf muscle
LL	In the same location where RL was placed, but on the left leg
V_1	In the fourth intercostal space (between ribs 4 and 5) just to the right of the sternum
V_2	In the fourth intercostal space (between ribs 4 and 5) just to the left of the sternum
V_3	Between leads V_2 and V_4
V_4	In the fifth intercostal space (between ribs 5 and 6) in the mid-clavicular line
V_5	Horizontally even with V_4, in the left anterior axillary line
V_6	Horizontally even with V_4 and V_5 in the midaxillary line

When placing electrodes on female patients, leads V3-V6 were always placed under the breast rather than on the breast.

Limb lead electrode were placed in fleshy areas on the inside of the arms and legs, near the wrist and ankle, avoiding bony prominences. Electrodes were placed equidistant from the heart and in approximately the same place on each limb. If a patient had an amputated portion of the limb, the electrode was placed on the fleshy area of the inside of the limb, as distal on the limb as possible. Electrode for the opposite limb were placed in the same altered position and recorded in the notes.

4. Final steps

Once the limb and chest electrodes were accurately and correctly placed, the lead wires were attached by fastening the clip of the wire to the electrode. Wires are color coded and labeled for each arm as LA, RA, for each leg as RL, LL, and for each chest lead, V1 through V6. The physician's interpretation can be affected if the lead wires are connected to the wrong electrodes, so EKG technician always checked the leads. The patient was informed that EKG is ready to be recorded and patient was asked to help by lying still and relaxing for just a moment while the study was in progress. Recorded EKG was printed and kept in the patient's chart.

5. Amplitudes and intervals

All the waves on an EKG tracing and the intervals between them have a predictable time duration, a range of acceptable amplitudes (voltages), and a typical morphology. Any deviation from the normal tracing is potentially pathological and therefore of clinical significance. For ease of measuring the amplitudes and intervals, an EKG was printed on graph paper at a standard scale: each 1 mm (one small box on the standard EKG paper) represents 40 milliseconds of time on the x-axis, and 0.1 millivolts on the y-axis.

TABLE 11 - Amplitudes and intervals.

Feature	Description	Pathology	Duration
P wave	The p-wave represents depolarization of the atria. Atrial depolarization spreads from the SA node towards the AV node, and from the right atrium to the left atrium	The p-wave is typically upright in most leads except for aVR; an unusual p-wave axis (inverted in other leads) can indicate an ectopic atrial pacemaker. If the p wave is of unusually long duration, it may represent atrial enlargement. Typically, a large right atrium gives a tall, peaked p-wave while a large left atrium gives a two-humped bifid p-wave	<80 ms
PR interval	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex. This interval reflects the time the electrical impulse takes to travel from the sinus node through the AV node	A PR interval <120 ms suggests that the electrical impulse is bypassing the AV node. A PR interval consistently >200 ms diagnoses first degree atrioventricular block	120 to 200 ms
QRS complex	The QRS complex represents the rapid depolarization of the right and left ventricles. The ventricles have a large muscle mass compared to the atria, so the QRS complex usually has a much larger amplitude than the P-wave	If the QRS complex is wide (>120 ms) it suggests disruption of the heart's conduction system, such as in LBBB, RBBB, or ventricular rhythms such as ventricular tachycardia. Hyperkalemia, or TCA overdose can also widen the QRS complex. An unusually tall QRS	80 to 100 ms

		complex may represent left ventricular hypertrophy while a very low-amplitude QRS complex may represent a pericardial effusion or infiltrative myocardial disease	
J-point	The J-point is the point at which the QRS complex finishes and the ST segment begins	The J point may be elevated as a normal variant. The appearance of a separate J wave or Osborn wave at the J point is pathognomic of hypothermia or hypercalcemia	
ST segment	The ST segment connects the QRS complex and the T wave; it represents the period when the ventricles are depolarized	It is usually isoelectric, but may be depressed or elevated with myocardial infarction or ischemia. ST depression can also be caused by LVH or digoxin. ST elevation can also be caused by pericarditis, Brugada syndrome, or can be a normal variant (J-point elevation)	
T wave	The T wave represents the repolarization of the ventricles. It is generally upright in all leads except aVR and lead V1	Inverted T waves can be a sign of myocardial ischemia, LVH, high intracranial pressure, or metabolic abnormalities. Peaked T waves can be a sign of hyperkalemia or very early myocardial infarction	160 ms

Corrected QT interval (QTc)	The QT interval is measured from the beginning of the QRS complex to the end of the T wave. Acceptable ranges vary with heart rate, so it must be corrected to the QTc by dividing by the square root of the RR interval	A prolonged QTc interval is a risk factor for ventricular tachyarrhythmias and sudden death. Long QT can arise as a genetic syndrome, or as a side effect of certain medications. An unusually short QTc can be seen in severe hypercalcemia	<440 ms
U wave	If the U wave is very prominent, suspect hypokalemia, hypercalcemia or hyperthyroidism	The U wave is hypothesized to be caused by the repolarization of the interventricular septum. It normally has a low amplitude, and even more often is completely absent	

3.3.2.2. GE MAC 5500 ELECTROCARDIOGRAPH SPECIFICATION

TABLE 12 - Technical specification of GE MAC 5500 EKG.

Feature	**Specification**
	Processing
EKG interpretation	Marquette 12SL EKG Analysis Program
Computerized Measurements	15-lead analysis includes measurements of user-selectable additional 3 leads
Optional	Hi-Res Late Potential Analysis and P-Wave Signal
Additional ECG Function	Vectorcardiography
EKG Analysis Frequency	500 samples/second (sps)
Digital Sampling Rate	16,000 samples/second/channel
Pre-Acquisition	Provides 10 seconds of instantaneous EKG acquisition
Dynamic Range	AC Differential ± 5mV, DC offset ±300 Mv
Resolution	4.88 µV/LSB at 250 sps, 4.88 µV/LSB at 500 sps
Frequency Response	–3 dB at 0.01 to 150 Hz
Common Mode Rejection	>140 dB (123 dB with AC filter disabled)
Input Impedance	>10MΩ at 10 Hz, defibrillator protected
Patient Leakage	<10 Ma
Pace Detection	Meets or exceeds ANSI/AAMI EC11-1991 standards
Pace Digital Sampling Rate	75,000 samples/second/channel
Pace Pulse Width	As low as 0.2 ms in duration
Pace Pulse Amplitude	As low as 0.5 mV in amplitude
Special Acquisition Function	Disconnected lead detection, electrode impedance, excessive AC noise, baseline wander, and muscle tremor messages
Heart Rate Meter	30 to 300 BPM ±10% or 5 BPM, whichever is greater. Heart rates outside

	this range will not be displayed
	Display
Display Type	10.4 in (264 mm) diagonal graphics backlit color AM LCD
Display Resolution	640 x 480 pixels with waveform enhancement
Display Data	Heart rate, patient name, ID, clock, waveforms, lead labels, speed, gain and filter settings, warning messages, prompts, and help messages
	Writer
Writer Technology	Thermal dot array
Writer Speeds	5, 12.5, 25, and 50 mm/s
Number of Traces	3, 6, 12, or 15 users selectable
Writer Sensitivity/Gain	2.5, 5, 10, 20, 10/5 (split calibration) mm/Mv
Writer Speed Accuracy	±2%
Writer Amplitude Accuracy	±5%
Writer Resolution	Horizontal 1000 dpi at 25 mm/s, 200 dpi vertical
Paper Type	Thermal, Z-fold, perforated, fan fold, 300 sheets/pack
Paper Size	A Size: 8.5 in x 11 in, (214.6 mm x 280 mm) A4 Size: 8.27 in x 11.7 in (210 mm x 297.5 mm)
	Keyboard
Type	Sealed elastomer with soft function keys, alphanumeric keys, writer controls, and TrimPad cursor controls
	Electrical
Power Supply	AC or battery operation
Voltage	100 to 240 VAC
Current	0.5A at 115 VAC, 0.3A at 240 VAC, typical, 0.85A max
Frequency	50 to 60 Hz
Battery Type	User replaceable, 18V at 3.5 AH ±10% rechargeable NiMH
Battery Capacity	100 single page reports, (typical) or six hours continuous display (without printing)
Battery Charge Time	Approximately 4.5 hours from total discharge (with display off)
	Hi-Res Late Potential Analysis and P-Wave Signal

Sensitivities Raw Data Template Average Beat Filtered Signals Vector Magnitude	 20 mm/mV 20 mm/mV 50 mm/mV 1 mm/Mv
Analysis Sampling Rate	1,000 samples/second/channel
Digital Sampling Rate	16,000 samples/second/channel
High/Low Pass Filters	Special filter using Fast Fourier Transform (FFT)
	Physical Specifications
Height	3.7 in (9.4 cm) with display closed
Width	15 in (38.1 cm)
Depth	13.8 in (35.1 cm)
Weight	Approximately 6.8 kg (15 lbs) including battery, without paper
	Environmental Specifications
Temperature Operating Transport/Storage	 50°to 104° F (10° to 40° C) –40°to 158° F (–40° to 70° C)
Humidity Operating Transport/Storage	 20% to 95% RH non-condensing 15% to 95% RH non-condensing
Pressure Operating Transport/Storage	 700 to 1060 hPA 500 to 1060 Hpa
	Magnetic Card Reader Specifications
Character Set	ANSI/ISO ALPHA alphanumeric characters and ANSI/ISO BCD (subset of ASCII [ISO 646 IRV:1991])
	Bar Code Scanner Specifications
Symbologies	Code 39 (extended), PDF-417, Code 128, Data Matrix, Interleaved 2 of 5
	Modular MAC Trolley Dimensions
Height	37 in (94 cm
Width	19 in (47 cm)
Depth	27 in (69 cm)

Height with Acquisition module holder	59 in (150 cm)
Weight	66 lbs. (30 kg)

3.3.3. ECHOCARDIOGRAPHY

3.3.3.1. PHYSICS AND INSTRUMENTATION

1. ULTRASOUND WAVES

Medical ultrasound imaging typically uses sound waves at frequencies of 1,000,000 to 20,000,000 Hz (1.0 to 20 MHz). In contrast, the human auditory spectrum comprises frequencies between 20 and 20,000 Hz [92]. Frequency and wavelength are mathematically related to the velocity of the ultrasound beam within the tissue (approximately 1,540,000 mm/s for human tissue) as indicated by the following equations:

Velocity of blood = Wavelength (mm) x frequency (Hz)

Wavelength (mm) = 1,540,000 mm/sec ÷ frequency (Hz)

Wavelength (mm) = 1.54 ÷ frequency (MHz)

The resolution of a recording varies directly with the frequency and inversely with the wavelength. High frequency, short wavelength ultrasound can separate objects that are less than 1 mm apart. Echocardiographic image resolution is generally 1 or 2 wavelengths. Thus, imaging with a 2.5-MHz transducer would result in a resolution of approximately 1 mm [93]. Imaging with higher frequency (and lower wavelength) transducers permits enhanced spatial resolution. However, because of attenuation, the depth of tissue penetration or the ability to transmit sufficient ultrasonic energy into the chest is directly related to wavelength and therefore inversely related to transducer frequency. The trade-off between tissue resolution

and penetration guides the choice of transducer frequency for clinical imaging. As an example, higher frequency transducers can be used in echocardiography for imaging of structures close to the transducer or the chest wall, such as the apex of the left ventricle with transthoracic imaging [92, 93, 94].

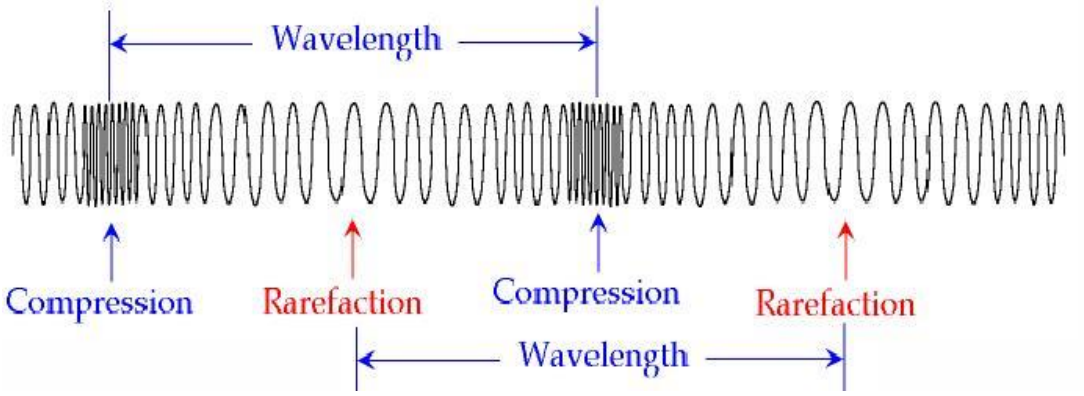

FIGURE 21 - Ultrasound physics refraction.

2. ULTRASOUND TRANSDUCERS

Ultrasound transducers use piezoelectric crystals to both generate and receive ultrasound waves. These crystals (quartz or titanate ceramic) alternately compress and expand the alternating electric current that is applied, thereby generating the ultrasound wave. Following a brief period of transmission, typically 1 to 6 microseconds, the same crystal also acts as a receiver. When a reflected ultrasound wave impacts the piezoelectric crystal, an electric current is generated. Image formation, which is related to the distance of a structure from the transducer, is based upon the time interval between ultrasound transmission and arrival of the reflected signal [94]. The amplitude is proportional to the incident angle and acoustic impedance, and timing is proportional to the distance from the transducer [92]. The simplest type of ultrasound transducer has a single piezoelectric crystal and is often used for M-mode recordings. 2D image requires mechanical or electronic sweeping of the ultrasound

beam across the plane of interest or sector. Initially, mechanical transducers physically moved a crystal. Phased-array transducers consist of a series of ultrasound crystals arranged so that they can be electronically steered, with no moving parts. In contrast to echocardiographic imaging, continuous-wave Doppler examinations utilize a pair of dedicated crystals: one for continuous transmission; and one for continuous receiving [95, 96]. The phased-array transducers commonly used in clinical echocardiography are showed on figure 22.

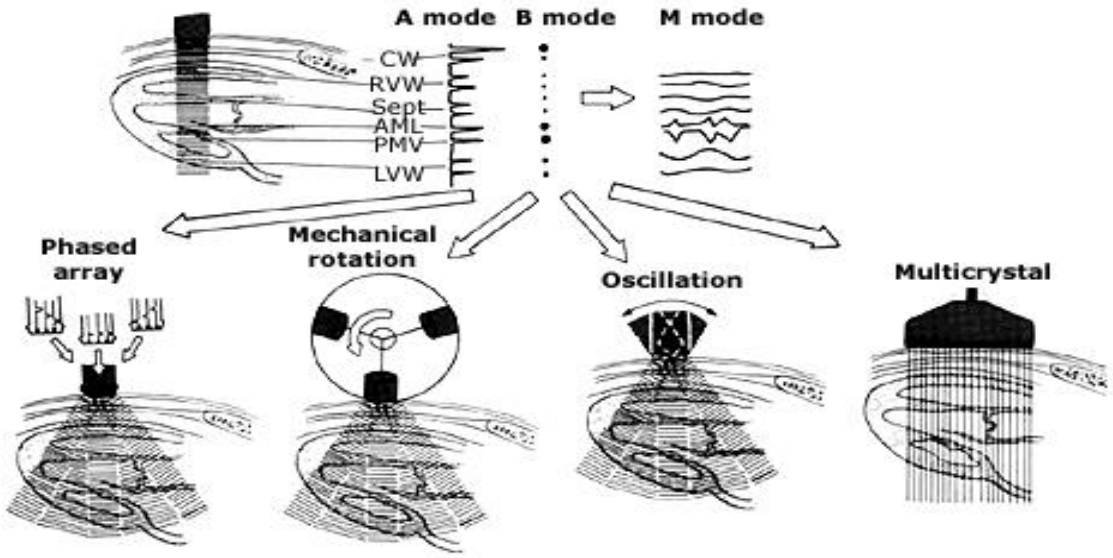

FIGURE 22 - Instrumentation of echocardiographic imaging. Anderson B, Wiley-Blackwell D. Echocardiography. Criticalecho.com (modified) [137].

3. RESOLUTION

Image resolution with 2D echocardiography can be considered in terms of:

● Axial resolution- function of the transducer frequency, bandwidth, and pulse length. Since the smallest resolvable distance between two specular reflections is 1 wavelength, higher-frequency transducers result in enhanced axial resolution. A wider bandwidth also improves resolution by allowing for a shorter pulse.

● Lateral resolution- varies with transducer frequency, beam width, bandwidth, aperture (width) of the transducer, and side lobes. At greater depths, beam width diverges so that a point target results in a reflected signal as wide as the beam width. Beam width artifacts appear as a bright linear structure.

3.3.3.2. ECHOCARDIOGRAM PERFORMANCE

A transthoracic echocardiogram Philips iE33 was used in the study. An echocardiogram was done by a specially trained ultrasound technician at patient's bedside in the hospital. The room was darkened to help the technician see the pictures on the monitor. The patient was asked to remove any jewelry and clothes above waist. All patients were imaged in the left lateral decubitus position. Electrodes were attached to patient's arms and legs to record the heart rate during the test. A small amount of gel was rubbed on the left side of the chest to help pick up the sound waves. A transducer was pressed firmly against the chest and moved slowly back and forth to provide specific views of the heart. This transducer sends sound waves into the chest and picks up the echoes as they reflect off different parts of the heart. The echoes were sent to a video monitor that recorded pictures of the heart for later viewing and evaluation. When the test was over, the gel was wiped off and the electrodes were removed. The test usually took from 30 to 60 minutes. All cardiologist who read echocardiograms were credentialed by the National Board of Echocardiography (NBE).

Patients were divided into 4 categories: patients without congestive heart failure, patients with any congestive heart failure if either systolic or diastolic function was compromised, patients with systolic CHF if ejection fraction was below 50% (Cardiologist at Albert Einstein Medical Center, Philadelphia use criteria of EF<50% to diagnose systolic CHF) and patients with only diastolic dysfunction (based on E/A ratio). Diastolic function was characterized according to severity. Mild diastolic dysfunction- abnormal LV relaxation- detected as a decrease in early diastolic flow velocity (E-wave) and a greater reliance on atrial contraction (A-wave) to fill the LV (E/A <1). Moderate diastolic dysfunction- "pseudonormalization"- which reflects an increase left atrial pressure at the onset of diastole and an increase in early diastolic flow velocity to a level near that of normal filling (E/A 1 to 1.5). Severe diastolic dysfunction- restrictive filling- which occurs when left atrial pressure is further elevated such that early diastolic flow is extremely rapid and left atrial and LV pressures equalize quickly during early diastole (E/A >2).

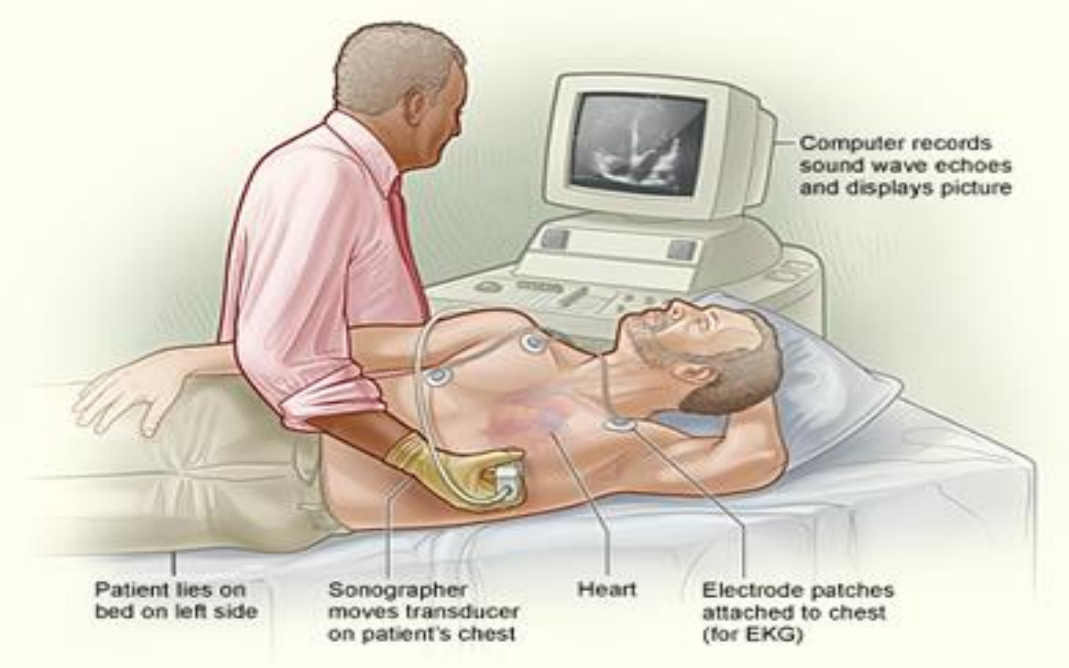

FIGURE 23 - Position during Echocardiography. The patient lies on his left side. A sonographer moves the transducer on the patient's chest, while viewing the pictures from the echocardiography on a computer. Echocardiography. www.nhlbi.nih.gov [138].

3.3.3.3. ECHOCARDIOGRAM SPECIFICATION

1) All examinations were performed with the Philips iE33 system with a 2-4 MHz transducer at a depth of 16 cm.

2) All patients were evaluated by transthoracic M mode, two dimensional (2D), pulsed wave (PW), continuous wave (CW), color flow and tissue Doppler imaging (TDI).

- **M-mode -** Motion echocardiography. A single crystal rapidly alternates between transmission and receiver modes with rapid updating (>1000 Hz); thus, rapidly moving structures (eg, valve leaflets) could be monitored for their characteristic motion. M-mode data was recorded and displayed on the video monitor at sweep speeds of 50 to 100 mm/sec. The very high temporal resolution permitted the identification of subtle abnormalities such as fluttering of the anterior mitral leaflet due to aortic regurgitation or movement of vegetation. In addition, dimensional measurements or changes, such as chamber size and endocardial thickening, were appreciated.

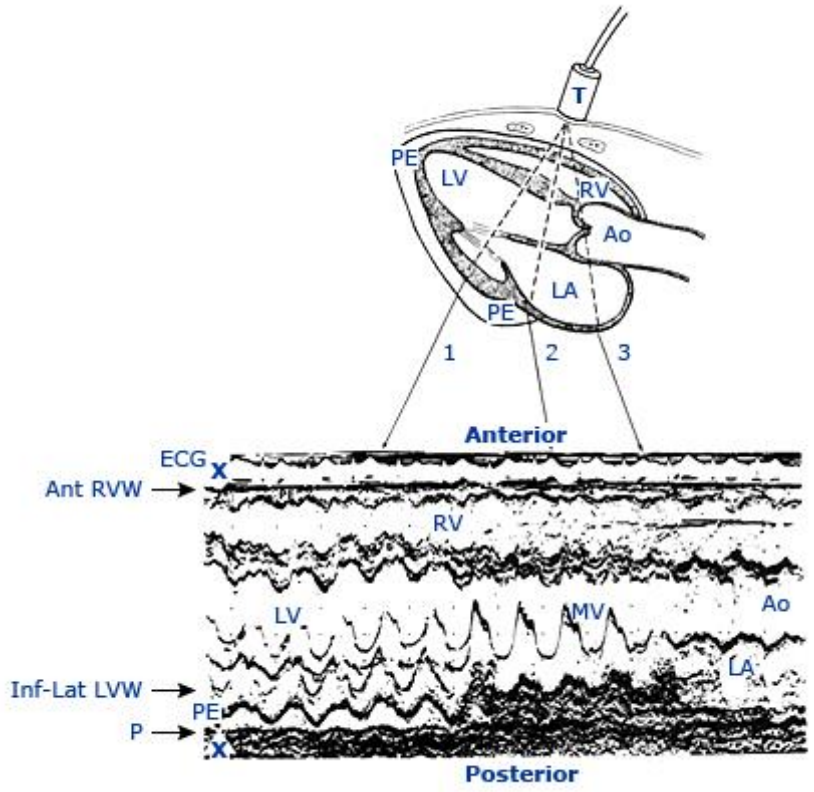

FIGURE 24 - M-mode echocardiographic examination of the heart in the parasternal long axis position. Grimm R, Thomas J. Transthoracic echocardiography**.** http://thoracickey.com [139]

- **Two-dimensional (2D) imaging** — image was generated from data obtained mechanically (mechanical transducer) and/or electronically (phased-array transducer). Since each scan line of data required a finite time for transmission and reception, the time required to complete each 2D image was directly related to the number of scan lines. Thus, there was a trade-off between scan line density and image frame rate. For cardiac applications, a high frame rate (at least 25 frames/second; 40 ms frame rate) was desirable for most situations. The signal received underwent a complex manipulation to form the final image displayed on the monitor including signal amplification, time-gain compensation, filtering, compression and rectification.

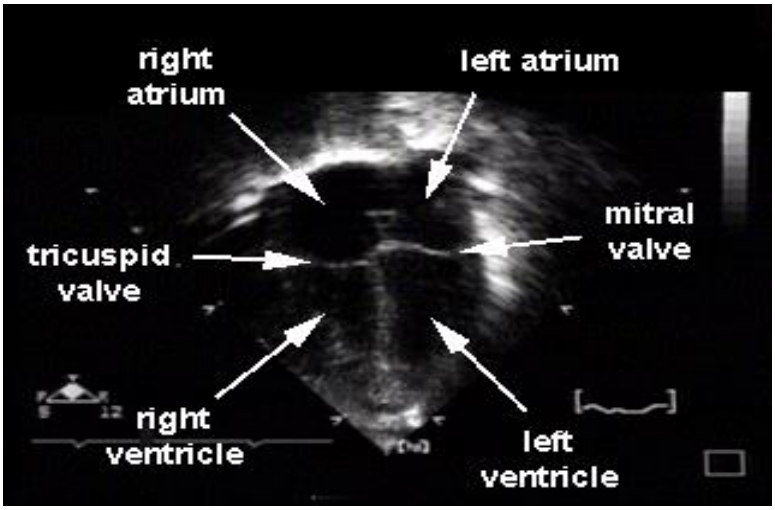

FIGURE 25 - Apical four-chamber view from a 2D echocardiogram of one of the patient included in the study (hypothyroid group).

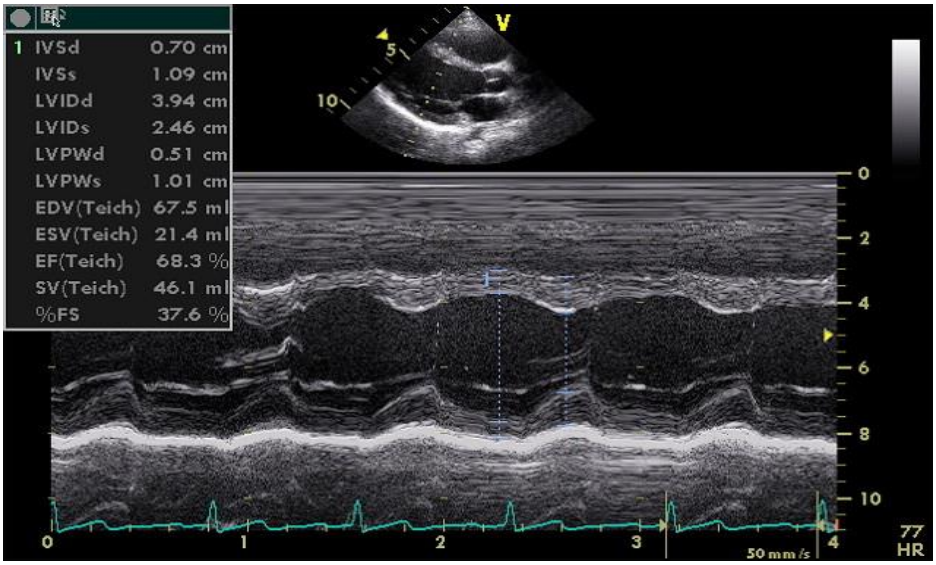

FIGURE 26 - Echocardiogram of one of the patient included in the study (hypothyroid group) in the parasternal long-axis view, showing a measurement of the heart's left ventricle.

- **Tissue Doppler echocardiography (TDE)** The technique uses frequency shifts of ultrasound waves to calculate myocardial velocity. It was used for assessment of left ventricular (LV) systolic and diastolic function, and estimation of LV filling pressures. Two techniques were used to assess myocardial function: pulsed-tissue TDE and color-coded TDE. The gate of the sample volume of pulsed-TDE was opened to 1 cm and directed to assess the region of interest, most often mitral annulus. For color-TDE, routine color flow instrumentation the autocorrelator technique was used to calculate and display multigated points of color-coded blood velocity along a series of ultrasound scan lines within a two-dimensional sector. Color-coded blood velocity data were then superimposed on conventional gray scale two-dimensional images in real time.

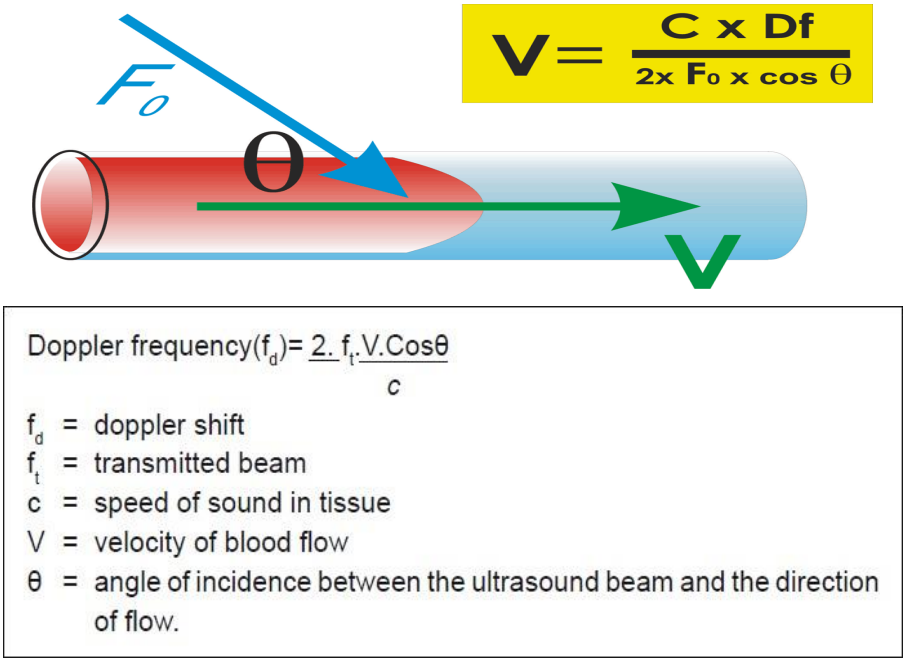

FIGURE 27 - Doppler Echocardiography. Sonovasc.com [140].

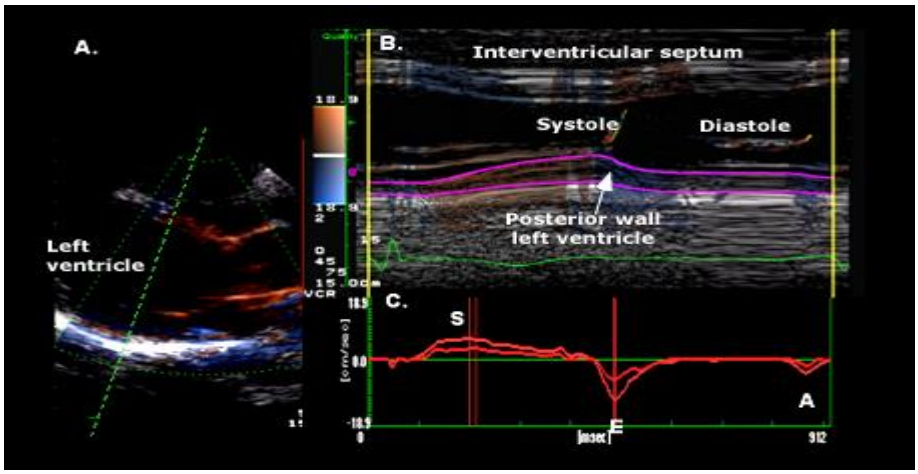

FIGURE 28 - Tissue Doppler echocardiographic image of normal left ventricle of one of the patient from the control group (euthyroid group). S: peak systolic velocity; E: peak early diastolic velocity; A: peak atrial velocity.

3) 2D and conventional Doppler examinations were obtained in the parasternal and apical views according to the guidelines of the American Society of Echocardiography and Canadian Cardiovascular Society/Canadian Society of Echocardiography Guidelines [97, 98, 99].

4) Left ventricular (LV) diameters and wall thickness were measured by M-mode echocardiography. LV ejection fraction (EF) was calculated using the apical two- and four-chamber views by Simpson's method, according to American Society of Echocardiography guidelines [98]. The mitral valve inflow pattern (E-wave, A-wave, E-wave deceleration time [Dt], E/A ratio and isovolumic relaxation time [IVRT]) were measured using pulsed wave Doppler. Cardiologist at Albert Einstein Medical Center, Philadelphia use criteria of EF<50% to diagnose systolic CHF

5) Transducer frequencies of 3.5 to 4.0 MHz performed Tissue Doppler imaging, adjusting the spectral pulsed Doppler signal filters to acquire the Nyguist limit of 15 to 20 cm/s.

6) Myocardial TDI velocities (peak systolic [Sm], early diastolic [Em] and late diastolic velocities [Am]) were measured via spectral pulsed Doppler as of the LV-free wall from the

apical four chamber view. The ultrasound beam was positioned as parallel as possible with the myocardial segment to acquire the optimal angle of imaging.

7) The time interval from the P wave onset on the surface of EKG to the beginning of the late diastolic wave (Am), which is defined atrial electromechanical coupling (PA). It was obtained from lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus and named as PA lateral, PA septum, and PA tricuspid respectively.

8) The difference between PA lateral and PA tricuspid was defined as inter-atrial electromechanical delay (EMD), and the difference between PA lateral and septum was defined as intra-atrial EMD.

TABLE 13 - Philips iE33 Echocardiogram specifications.

System specification	
Foot print (H x W x D) 150cm x 56cm x 110cm Weight 345 Ibs	
User interface	
Monitor size 20” LCD Flat Panel Moveable console Adjustable monitor 500 fps 2D Frame Rate 250 fps Color Frame Rate Pre-processing	Post-processing 2-30cm Display Depth Selectable Dynamic Range Adjustable Transmit Focus 3 Transducer Ports
Imaging Models	
2D	M-Mode
Doppler Models	
High Frame Rate Color Flow Color Doppler Velocity Color Flow Mapping Color Doppler Energy Color Power Doppler	Directional Color Power Doppler Directional Tissue Imaging (DTI) Pulse Wave (PW) Continuous Wave (CW)
Software Technologies	
3D imaging Compounding Speckle reduction Tissue Harmonic Imaging (THI) Auto gain/ Optimization Panoramic Imaging	Dual imaging Split Screen Duplex Triplex Clip Foundation

Connectivity Ports	
USB	VHS
DVI	EKG
Image File Format	
AVI	JPEG
DICOM	
Onboard/External Storage	
CD/DVD	Hard Drive 160 GB
Cine Clips	
Power Supply	
AC 100-240V, 50/60 Hz	
Peripherals	
DICOM	EKG

3.3.4. BIOTELEMETRY

Biotelemetry (or Medical Telemetry) involves the application of telemetry in the medical field to remotely monitor various vital signs and cardiac rhythm of hospitalized patients. Telemetry is the automatic measurement and wireless transmission of data from remote sources. Sensors at the source measure either electrical data (such as voltage or current) or physical data (such as temperature or pressure). These measurements are converted to specific electrical voltages. A multiplexer combines the voltages, along with timing data, into a single data stream for transmission to a remote receiver. Upon reception, the data stream is separated into its original components and the data is displayed and processed according to user specifications.

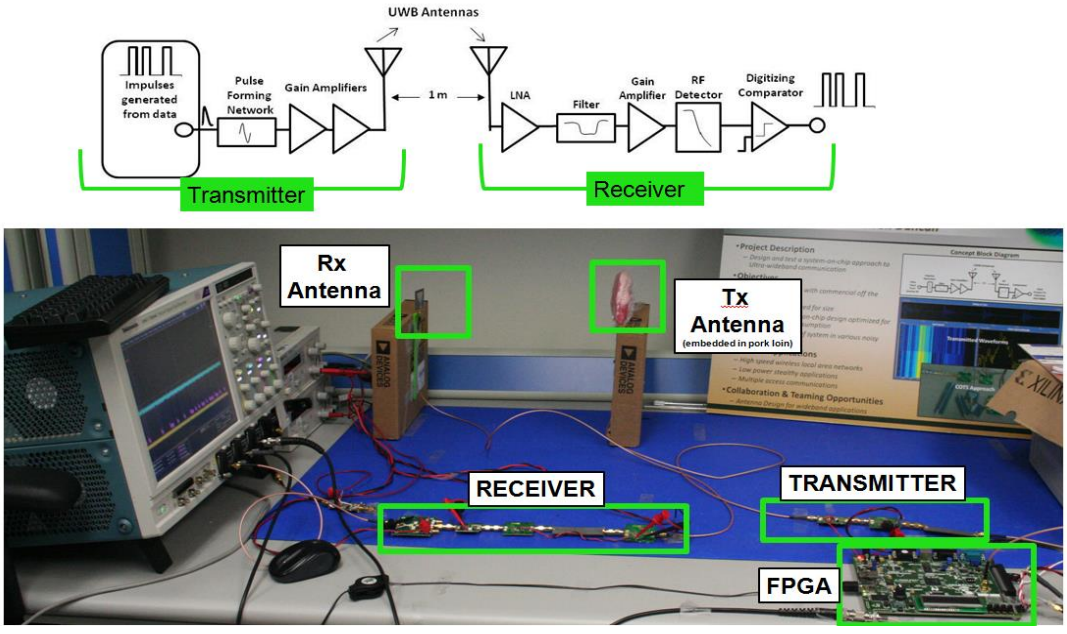

FIGURE 29 - Basic telemetry system.

Using telemetry, patients are monitored continuously and unobtrusively for 24 hours a day by certified monitoring technicians who analyze the data and if there is any abnormalities and/or arrhythmia, they notify a cardiologist immediately. This information is not only helpful in diagnosis and treatment, but also if there is a life-threatening arrhythmia, the appropriate intervention can be taken without any delays. The sooner arrhythmias are recognized and treatment is offered, the better prognosis for the patient.

3.3.4.1. BIOTELEMETRY PROCEDURE

The Charter Kontron Telemetry Monitoring System and Enguard View system were used in the study. All patients were informed that the process is painless, but can be slightly uncomfortable because the patient must wear the electrodes all the time during hospitalization. They were also informed that if they notice loose connections of the leads or if leads become unplugged for any reason they should bring it to the nurse's attention immediately.

Generally, the transmitter box is small, about the size of a cell phone and it fits into a pocket in the person's gown. Wearing a portable transmitter allowed patients to be very mobile, as long as the signal stayed in the range of the monitoring station. Patients could do simple things, such as use the bathroom, without the help of a caregiver.

The Charter Kontron Telemetry Monitoring System contains 4 parts:

- Sensor
- Battery-powered, patient worn transmitter
- A Radio Antenna and Receiver
- A display unit capable of concurrently presenting information from multiple patients

A) B)

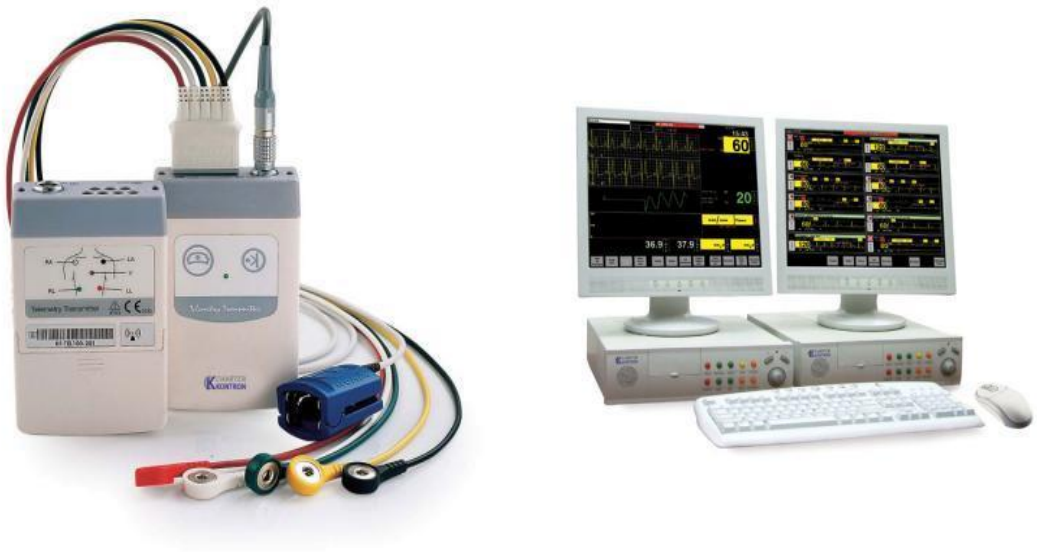

FIGURE 30 - Charter Kontron Telemetry Monitoring System used in the study. A) The transmitter B) Enguard View system.

The patient was wearing 5 electrodes on the chest that were attached to leads and a telemetry transmitter**.** The sensor was sending an EKG information about every heartbeat to a portable transmitter. The transmitter was sending signals constantly to 2 monitoring stations:

- one in the nurses' station where they could be watched directly by nurses and cardiologists
- and the second one in the telemetry room, where certified monitoring technicians were monitoring the electrical activity of the heart.

3.3.4.2. ELECTRODE POSITIONING FOR CARDIAC MONITORING

In contrast to the standard 12-lead EKG in which limb electrodes are placed on wrists and ankles, at bedside cardiac monitoring limb electrodes were placed on the torso to reduce muscle artifact during limb movement and to avoid tethering the patient. The 4 limb electrodes were placed in the LA, RA, LL, and RL positions so that any of the 6 limb leads could be obtained (leads I, II, III, aVR, aVL, or aVF). A fifth chest electrode was placed in V_1 locations (it was chosen due to high value of V1 in arrhythmia monitoring). Cardiac monitors with this lead system had 2 channels for EKG display so that 1 limb lead and 1 precordial lead could be displayed simultaneously.

Descriptions of lead systems:

- the right arm (RA) electrode was placed in the infraclavicular fossa close to the right shoulder,
- the left arm (LA) electrode was placed in the infraclavicular fossa close to the left shoulder,
- the left leg (LL) electrode is placed below the rib cage on the left side of the abdomen,
- the ground or reference electrode (RL) was placed on the right side of the abdomen,
- cardiac monitor (C) was placed in V1 position.

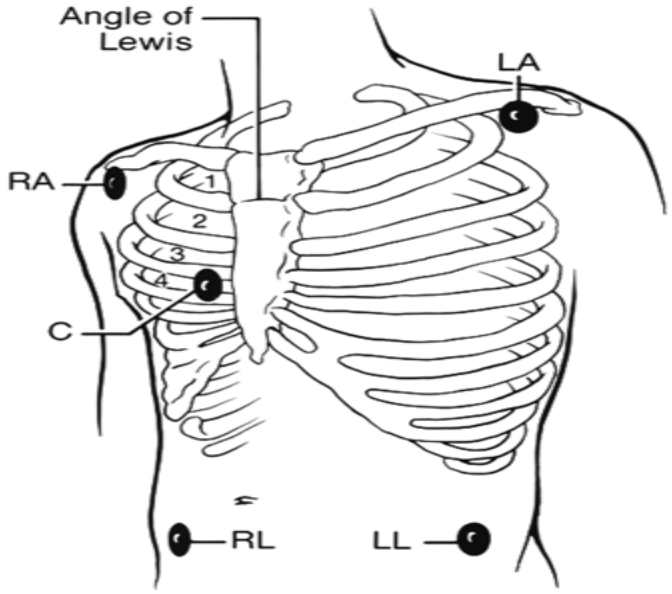

FIGURE 31 - 5-electrode lead system that allows for recording any of the 6 limb leads plus 1 precordial (V) lead. RA-right arm, LA-left arm, LL-left leg, RL-right leg, C-cardiac. Drew B, Califf M, Funk M, et al. Practice standards for electrocardiographic monitoring in hospital settings. *Circulation*, 2004;110:2721-2746 [141].

TABLE 14 - Charter Kontron Telemetry Monitoring System specifications.

Telemetry Transmitter Features
ECG transmission of seven vectors using standard 5 lead cable
Automatic ECG cable 3 / 5 identification
SpO2 telemetry
Nurse call button on the transmitter
Event button on the transmitter
96 hour of ECG transmission, using only 2 AA batteries
48 hours for transmission of both ECG and SpO2
Central Nurse Station telemetry features
Continuous display of 3 ECG leads
Seven leads ECG, I, II, III, aVR, aVL, aVF, V available on request
Heart rate display with heart rate alarm
Dual lead ST measurement
Arrhythmia alarms
Full disclosure of last 48 hours
Audio nurse call at central station
Battery status and signal quality displayed at Central Nurse Station
Additional Central Nurse Station features
Simultaneous display of up to 32 monitors, telemetry or bedside
Alarm monitoring of up to 64 monitors, telemetry or bedside
Central Station may display data from the telemetry monitors in addition to all
Charter Kontron patient monitors: Enmove, Envoy, and VitaLogik

3.3.4.3. ENGUARD VIEW SYSTEM

It is high-end central station combining Ensemble CNS and Enguard Remote Workstation systems, to create the optimal solution for multi-tasking nurse station. This dual-screen system provides a simultaneous view of 12 patients from the available beds on the network with a full display of any individual patient monitor. This system allows monitoring of patients in different areas from a single central station.

The Enguard View central station provides access to all monitors and data throughout the monitoring network, providing a comprehensive view of patient data, including:

- Full Disclosure
- Graphical Trends
- Numerical Charts
- Arrhythmia Analysis
- ST Watch
- Patient Reports

4. RESULTS

4.1. GROUP CHARACTERISTICS

4.1.1. CHARACTERISTICS OF THE STUDY GROUP (HYPOTHYROID GROUP)

After applying exclusion criteria, 152 patients from 214 potential subjects for the study, met inclusion criteria and were selected as the hypothyroid group. Mean TSH ± SD (standard deviation) in this group was 40.4 ± 44.68 μIU/mL (95 % CI 33.3-47.5). Range of TSH was 10.09 (the lowest) to 304 (the highest) μIU/mL.

Group characteristic:

1. Age:

Mean age in the study group was 61.9 ± 19.2 years old. The youngest patient was 20 years old, the oldest was 96 years old. Mean age in females was 61.0 ± 20.1 years old and mean age in males was 64.4 ± 16.3 years old.

2. Gender:

-females: 111 patients (73%)

-males: 41 patients (27%)

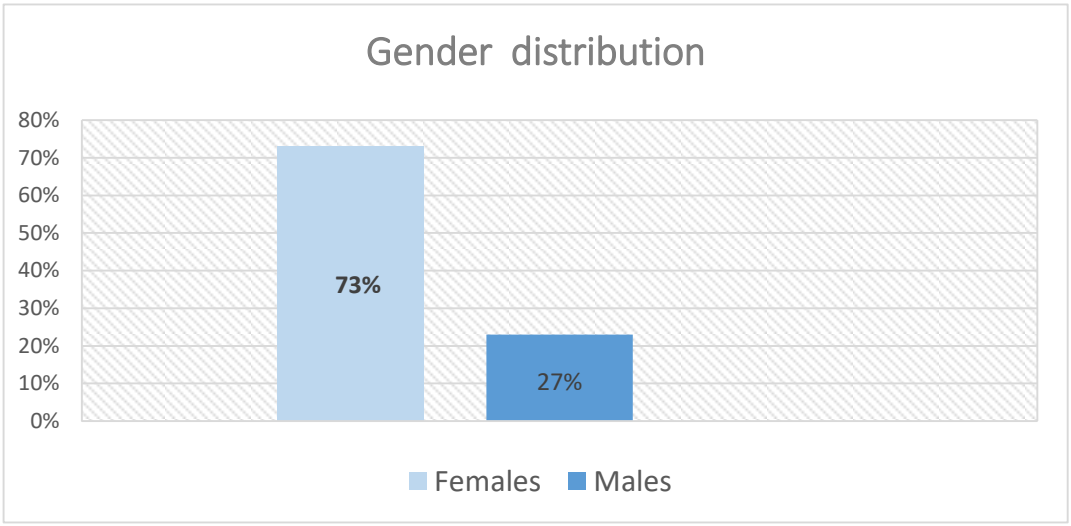

FIGURE 32 - Gender distribution in hypothyroid group in percentage.

3. Ethnicity:

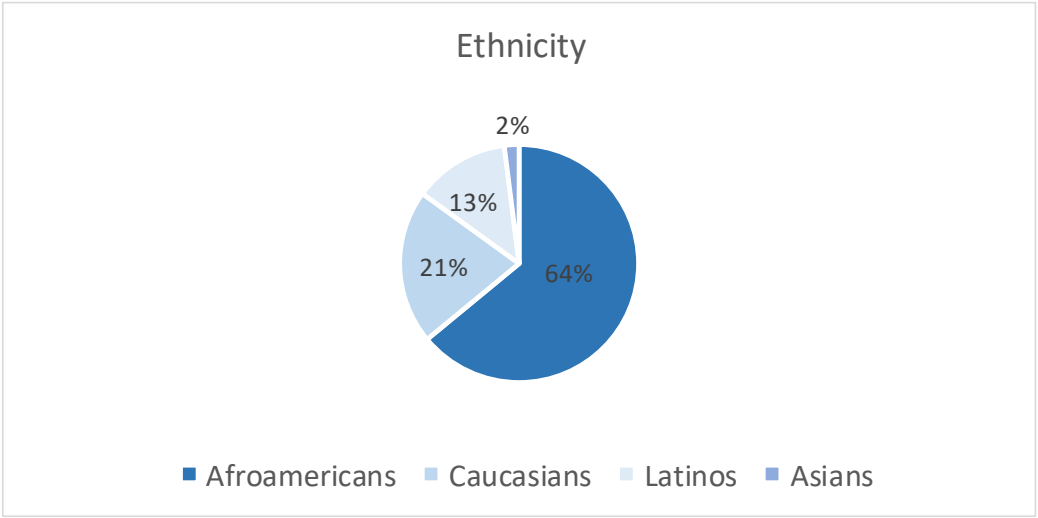

FIGURE 33 - Ethnicity distribution in hypothyroid group in percentage.

4.1.2. CHARACTERISTICS OF THE CONTROL GROUP (EUTHYROID GROUP)

152 patients met inclusion criteria for the euthyroid group. Mean TSH in this group was 0.89 μIU/mL ± 0.43 (95 % CI 0.82-0.96). Range of TSH was 0.55 (the lowest) to 2.85 (the highest) μIU/mL.

Group characteristic:

1. Age:

Mean age in this group was 61.9 ± 19.2 years old. The youngest patient was 20 years old, the oldest 96 years old. Mean age in females was 60.9 ± 20.0 years old and mean age in males was 64.9 ± 16.5 years old.

2. Gender:

-females: 111 patients (73%)

-males: 41 patients (27%)

3. Ethnicity:

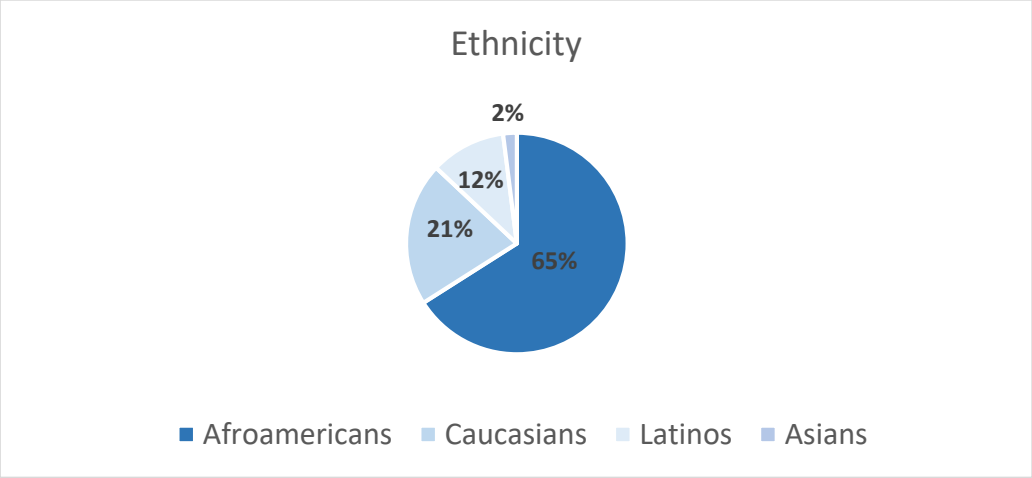

FIGURE 34 - Ethnicity distribution in euthyroid group in percentage.

4.2. HISTORY OF CONGESTIVE HEART FAILURE

Left ventricular systolic and diastolic function were evaluated based on transthoracic echocardiogram result, chest x-ray, physical exam and elevated B-type natriuretic peptide (BNP) level. Patients were classified into four categories:

1) Normal ejection fraction (>50%) and no diastolic dysfunction-no congestive heart failure.
2) Any congestive heart failure if either systolic or diastolic function was compromised.
3) Systolic CHF if ejection fraction was below 50%.
4) Only diastolic dysfunction per Echocardiography report.

There were 60 patients (39%) with any congestive heart failure in the hypothyroid group and 69 patients (45%) in the euthyroid group. The difference was not statistically significant with p-value 0.29. There was no statistically significant difference between prevalence of systolic CHF, 23 patients (15%) in the study group vs 19 patients (12%) in the control group (p-value 0.51). Diastolic dysfunction with preserved ejection fraction was diagnosed in 37 patients (24%) from the hypothyroid group and in 50 patients (33%) from the control group with p-value 0.09.

There was no statistically significant correlation between type of congestive heart failure and type of arrhythmia.

Types of CHF (in percentage) are presented on Figure 35 (hypothyroid group) and Figure 36 (euthyroid group).

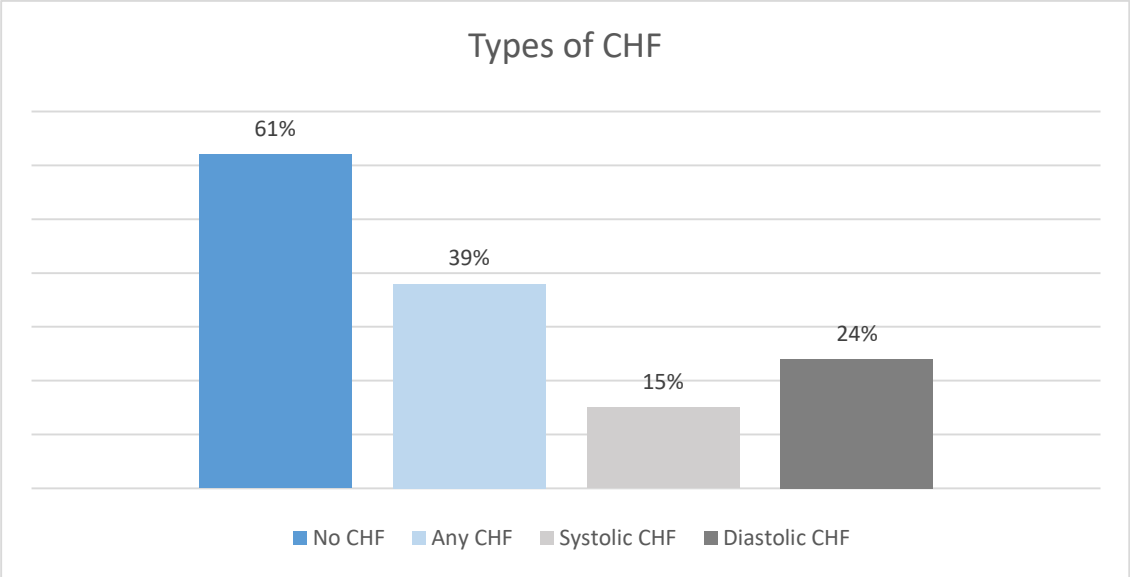

FIGURE 35 - Types of CHF in hypothyroid patients in percentage.

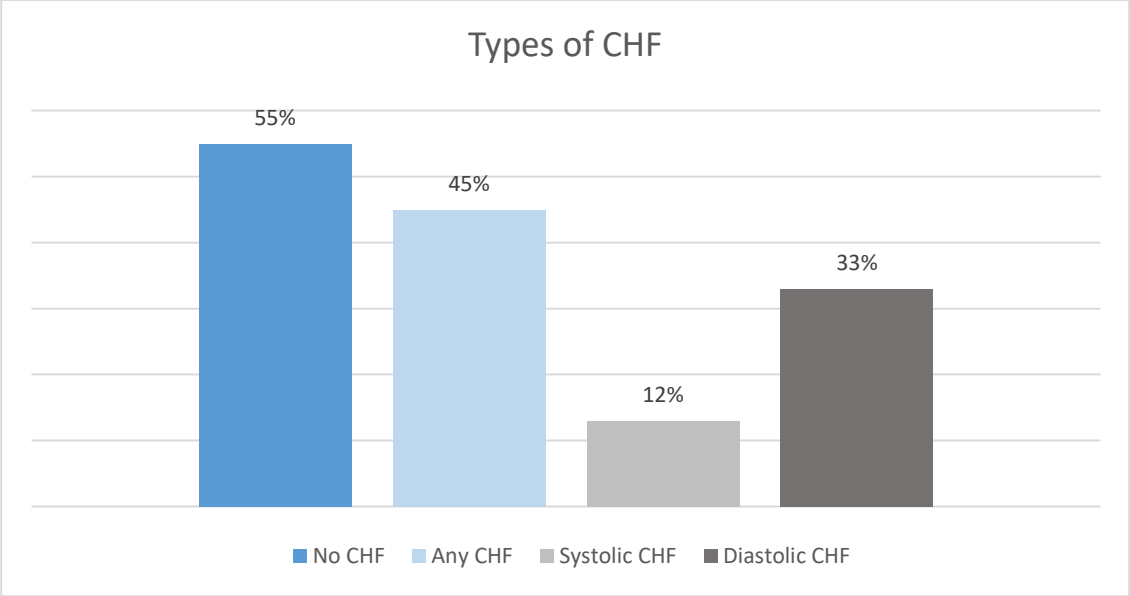

FIGURE 36 - Types of CHF in euthyroid patients in percentage.

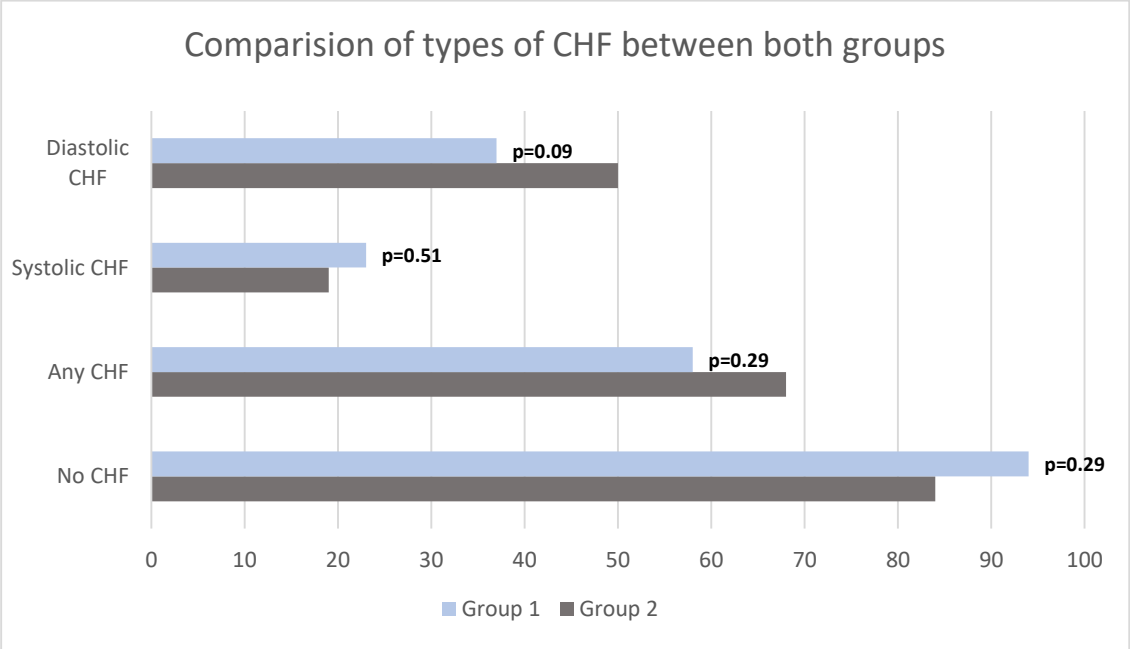

FIGURE 37 - Comparison of types of CHF between both groups (number of patients). Group 1- hypothyroid group, group 2-euthyroid group (control group).

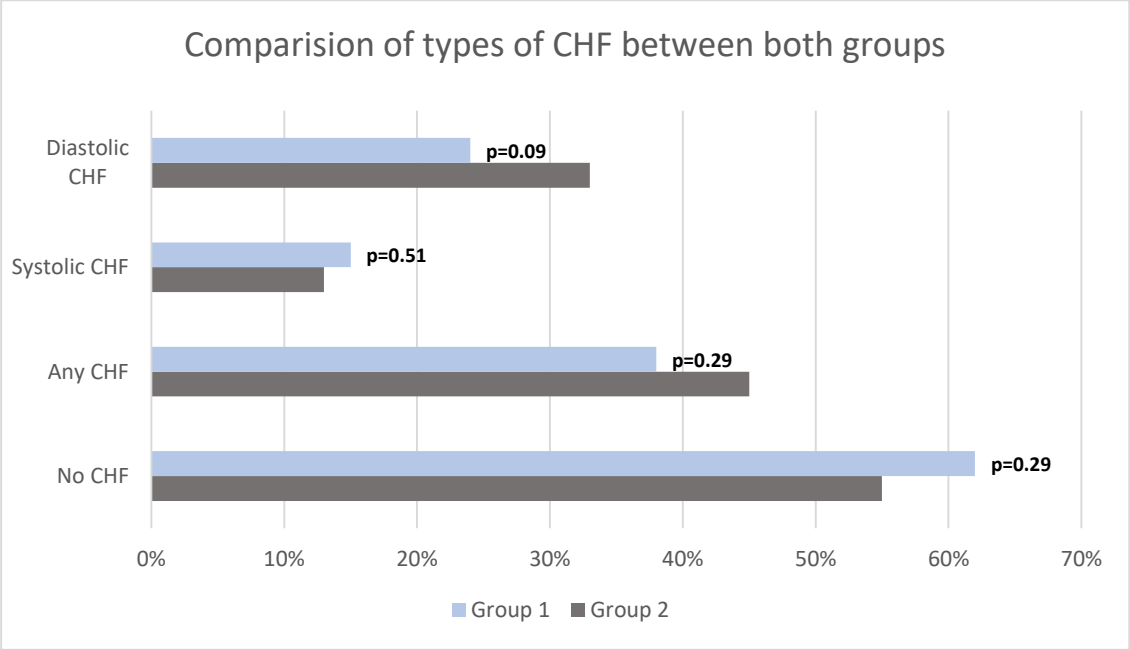

FIGURE 38 - Comparison of types of CHF between both groups in percentage. Group 1- hypothyroid group, group 2-euthyroid group (control group).

4.3. ARRHYTHMIAS

Data regarding specific arrhythmias were obtained from the EKG, chart documentation of known past medical history and from telemetry recordings during the hospitalization. History of cardiac arrhythmias included:

A) Tachyarrhythmias:

- atrial fibrillation (AFib)
- atrial flutter (AF)
- atrial tachycardia
- atrioventricular reentrant tachycardia (AVRT)
- atrioventricular node reentrant tachycardia (AVNRT)
- ventricular tachycardia (VT)
- nonsustained ventricular tachycardia
- ventricular fibrillation (VF)

B) Bradyarrhythmias:

- sinus bradycardia
- atrioventricular block (AVB)
- junctional rhythms
- idioventricular rhythm

There was no statistically significant correlation between TSH level and type of arrhythmia. Any arrhythmias were noticed in 69 patients in the hypothyroid patients and only in 55 patients from the control group, however it was not statistically significant (p=0.10).

The frequencies of individual arrhythmias in the entire study population, and in both groups (hypothyroid and euthyroid group) separately are summarized in table 15, table 16 and table 17, respectively.

TABLE 15 - The frequencies of arrhythmias in the entire study population.

Arrhythmia	Frequency in the entire study population n=304 (%)
Any arrhythmia	40.7%
Any SVT*	19.1%
Any Ventricular arrhythmia	3.9%
SVT*	2%
Atrial fibrillation	13.5%
Atrial flutter	3.6%
Atrioventricular block	11.8%
Junctional rhythm	5.6%
VT*	1.3%
NSVT*	2%
Ventricular fibrillation	0.7%
Idioventricular rhythm	0.3%

*SVT-Supraventricular Tachycardia, VT-Ventricular Tachycardia, NSVT-Nonsustained Ventricular Tachycardia

TABLE 16 - Comparison of the frequencies of individual arrhythmias in hypothyroid group and euthyroid group (control group).

	Hypothyroid n=152 (%)	**Euthyroid n=152** (%)	**P-Value**
Any arrhythmia	45.4%	36.2%	0.10
Any SVT*	18.4%	19.7%	0.77
Any Ventricular arrhythmia	**6.6%**	**1.3%**	**0.02**
SVT*	2%	2%	1.00
Atrial fibrillation	13.8%	13.2%	0.86
Atrial flutter	2.6%	4.6%	0.35
Atrioventricular block	12.5%	11.2%	0.72
Junctional rhythm	7.2%	3.9%	0.2
VT*	**2.6%**	**0%**	**0.04**
NSVT*	2.6%	1.3%	0.41
Ventricular fibrillation	1.3%	0%	0.15
Idioventricular rhythm	0.7%	0%	0.31

*SVT-Supraventricular Tachycardia, VT-Ventricular Tachycardia, NSVT-Nonsustained Ventricular Tachycardia

TABLE 17 - The frequencies of individual arrhythmias in hypothyroid group and euthyroid group (control group) (number of patients).

	Hypothyroid (number of patients)	**Euthyroid** (number of patients)	**P-Value**
Any arrhythmia	69	55	0.10
Any SVT*	28	30	0.77
Any Ventricular arrhythmia	**10**	**2**	**0.02**
SVT*	3	3	1.00
Atrial fibrillation	21	20	0.86
Atrial flutter	4	7	0.35
Atrioventricular block	19	17	0.72
Junctional rhythm	11	6	0.2
VT*	**4**	**0**	**0.04**
NSVT*	4	2	0.41
Ventricular fibrillation	2	0	0.15
Idioventricular rhythm	1	0	0.31

*SVT-Supraventricular Tachycardia, VT-Ventricular Tachycardia, NSVT-Nonsustained Ventricular Tachycardia

ATRIAL ARRHYTHMIAS

There was no difference in prevalence in any supraventricular tachycardia (SVT) between both groups (28 vs 30 patients, p=0.77). Atrial fibrillation was diagnosed in 21 patients in the hypothyroid group and in 20 patients in the euthyroid group (p=0.86). Atrial flutter was found in 7 patients in the control group and in 4 patients in the study group (p=0.35).

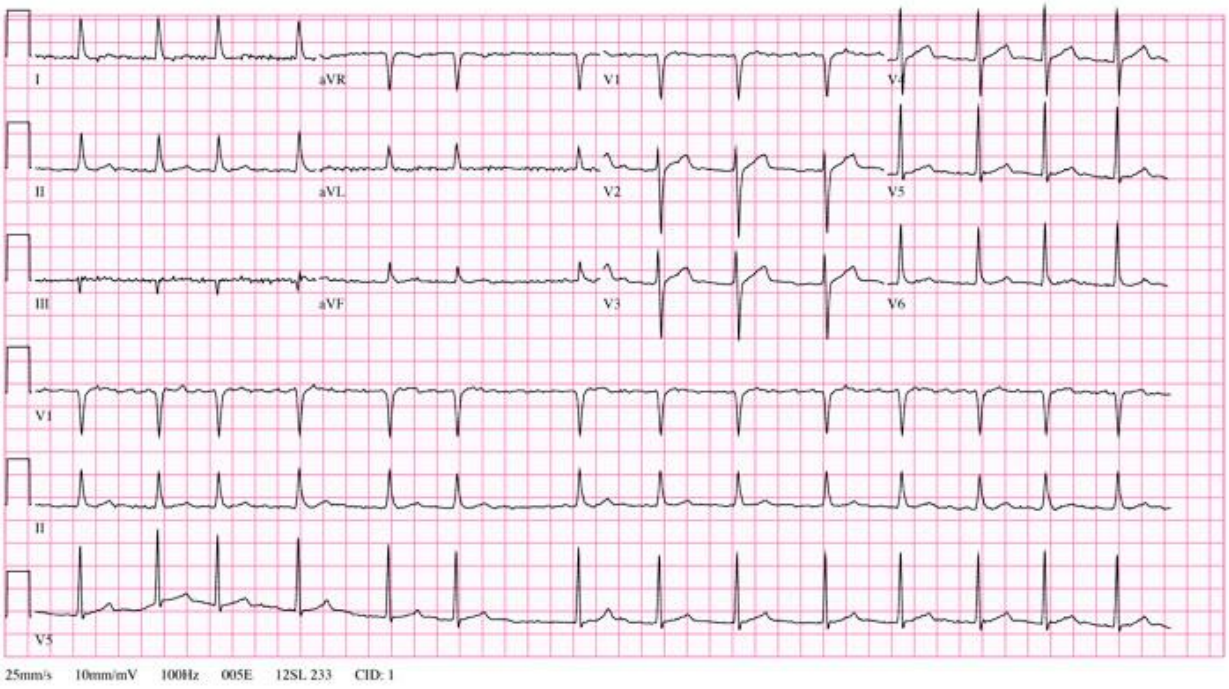

FIGURE 39 - Atrial Fibrillation in one of the patients from the hypothyroid group.

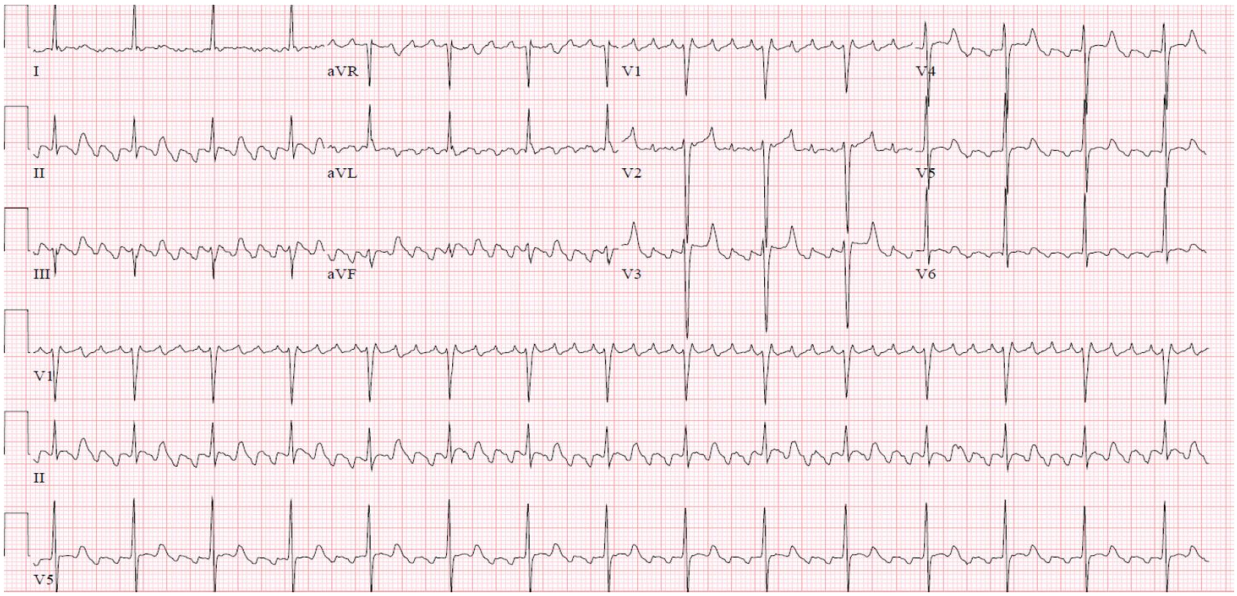

FIGURE 40 - Atrial Flutter in one of the patients from the euthyroid group.

Junctional rhythm was present almost twice as often in patients with hypothyroidism than in patients with normal thyroid function. There were 11 patients with junctional rhythm in Group 1 and only 6 patients in the control group, however it was not statistically significant (p=0.2).

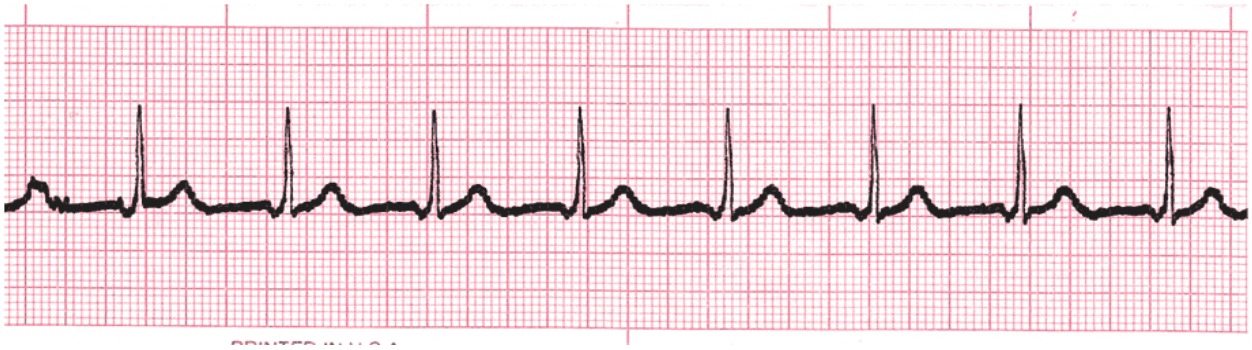

FIGURE 41 - Junctional rhythm registered on telemetry monitor in one of the patients with hypothyroidism.

VENTRICULAR ARRHYTHMIAS

Any ventricular arrhythmia occurs more frequently in the study group than in the control group and it was statistically significant (10 patients vs 2 patients respectively, p=0.02). Nonsustained ventricular tachyarrhythmia (NSVT) was twice more common in the hypothyroid patients (4 patients) than in the euthyroid patients (2 patients), but it was not statistically significant (p=0.41). Life threatening arrhythmia, ventricular fibrillation (VF) was noticed in 2 patients from the hypothyroid group and in none of the patients from the control group. The difference was not statistically significant with p-value 0.15. Both patients died, despite performing aggressive resuscitation measurement. Also, idioventricular rhythm was recorded on a telemetry monitor in 1 patient with hypothyroidism and in none of the patients with normal thyroid function, however it was not statistically significant (p=0.31).

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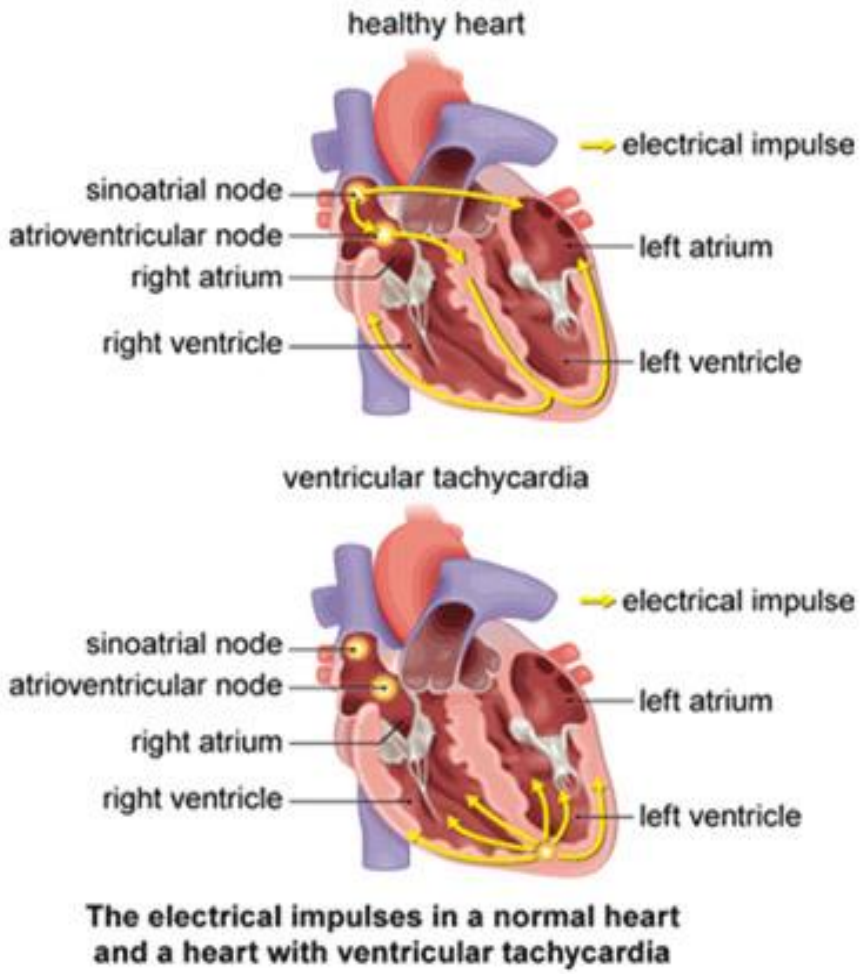

FIGURE 42 - The electrical impulses in a normal heart and a heart with ventricular tachycardia. Modified from Bupa.co.uk.

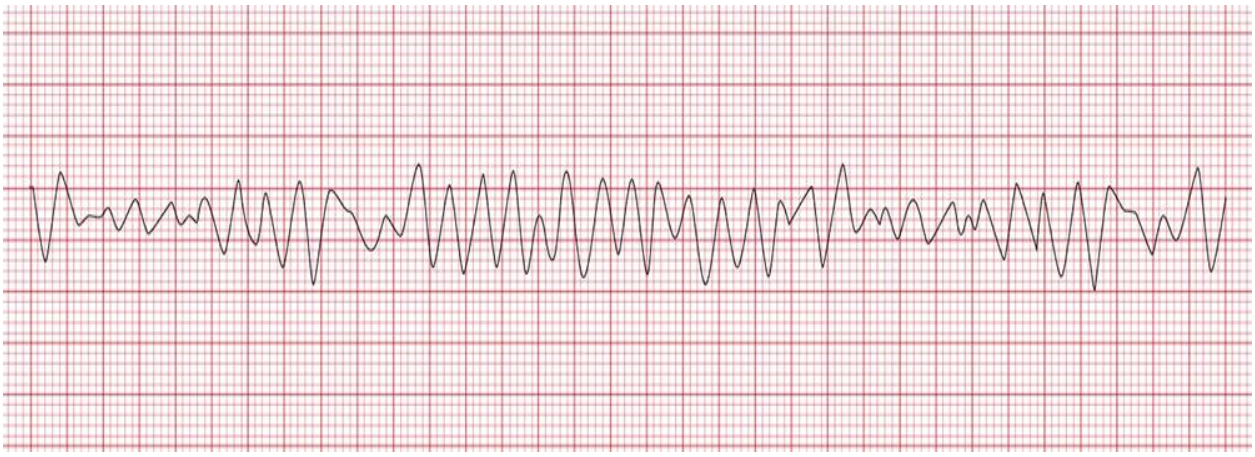

FIGURE 43 - Ventricular fibrillation (VF) printed from a telemetry monitor in one of the patients from hypothyroid group.

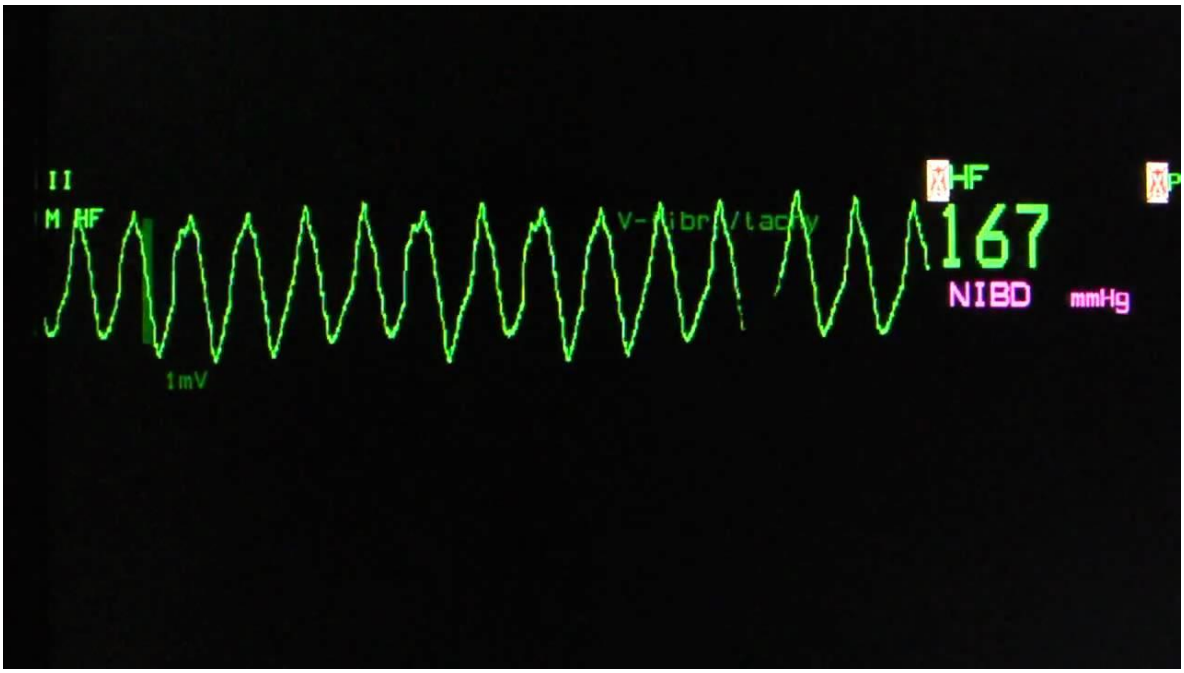

FIGURE 44 - Picture of a telemetry monitor (lead II) one of the patients from hypothyroid group during code blue. Lethal Ventricular fibrillation (VF).

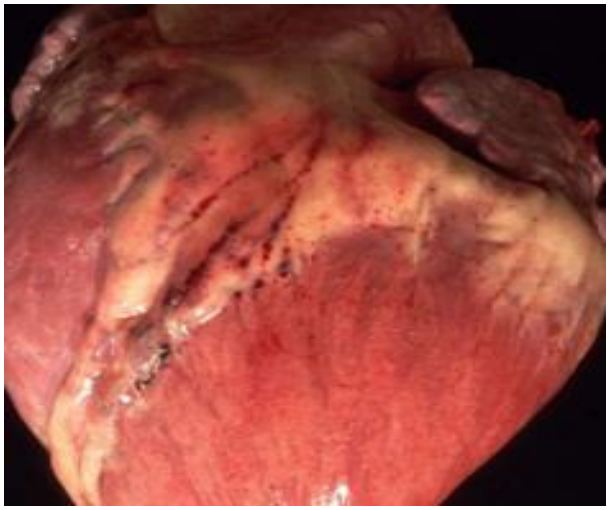

FIGURE 45 - Postmortem heart one of the patients from hypothyroidism group who died from ventricular fibrillation. Petechial pericoronal haemorrhages and necrosis/hyalinosis of myocytes are seen.

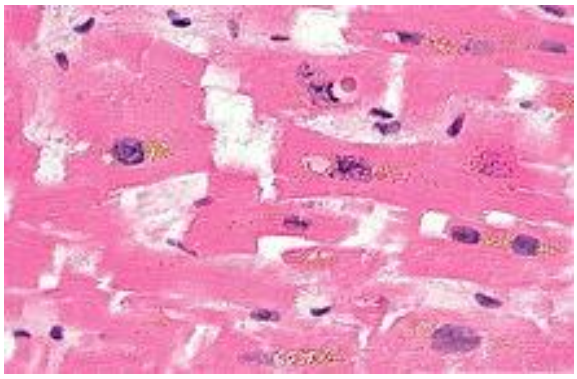

FIGURE 46 - Histopathology (H&E stain) of the heart of the same patient. Myofibre break-up with squared nuclei, a morphologic correlate of ventricular fibrillation.

SUMMARY:

1) There were 304 subjects included in the study who were divided into 2 groups comprising 152 subjects in each arm of the study. Each hypothyroid patient was age, gender and race matched against the euthyroid subject.

2) Mean age in the hypothyroid group was 61.9 ± 19.2 years old and 61.9 ± 19.2 years old in the euthyroid group.

3) In the hypothyroid group mean age in females was 61.0 ± 20.1 years old and mean age in males was 64.4 ± 16.3 years old. In the euthyroid group mean age in females was 60.9 ± 20.0 years old and mean age in males was 64.9 ± 16.5 years old.

4) Mean TSH in hypothyroid group was 40.4 ± 44.68 μIU/mL (95 % CI 33.3-47.5) and 0.89 ± 0.43 μIU/mL (95 % CI 0.82-0.96) in the hypothyroid group.

5) Chi-square analysis revealed a higher prevalence of ventricular tachycardia (p-value 0.04) and any ventricular arrhythmia in hypothyroid group (p-value 0.02).

6) There were 2 patients with ventricular fibrillation in hypothyroid group and none of the patient from control group had ventricular fibrillation, however there was no statistically significant difference (p-value 0.15). Unfortunately, both arrhythmias were fatal despite performing aggressive resuscitation measurements.

7) Junctional rhythm was present almost twice as often in patients with hypothyroidism than in patients with normal thyroid function, however it was not statistically significant (p-value 0.2).

8) Limitations to the current study include its retrospective nature, limited sample size and fact that hypothyroidism was diagnosed based on one measurement of TSH and fT4 level with unknown etiology of hypothyroidism.

5. DISCUSSION

It is well known that hypothyroidism affects cardiac functions and have various cardiovascular manifestations including impaired diastolic functions, reduced contractility and infrequent pericardial effusion and heart failure. It is widely accepted that by acting on cardiac myocyte gene expression thyroid hormones exert transcriptional regulation [100]. Other non-transcriptional effects of the thyroid hormone, include regulation of intracellular levels of calcium and potassium in myocytes. Thyroid hormones affect calcium uptake by the sarcoplasmic reticulum, to stimulate plasma membrane Ca-ATPase activity and to increase voltage-dependent channels in ventricular cells [101, 102]. These effects together modulate the function of the myocardium. Thyroid dysfunction is also associated with electrophysiological remodeling of the heart [3]. Therefore, slight changes in blood levels of thyroid hormones have many adverse effects on both function and structure of the cardiovascular system.

The hemodynamic effects of hypothyroidism are opposite to those of hyperthyroidism, although the clinical manifestations are less obvious. The most common signs are: bradycardia, mild hypertension, a narrowed pulse pressure, and attenuated activity on the precordial examination. Pericardial effusion and nonpitting edema (myxedema) can occur in patients with severe, long-standing hypothyroidism. Low cardiac output is caused by bradycardia, decreased ventricular filling, and decreased cardiac contractility. Systemic vascular resistance may increase by as much as 50 percent, and diastolic relaxation and filling are slowed. Heart failure is still very rare, because the cardiac output is usually sufficient to meet the lowered demand for peripheral oxygen delivery. Positron emission tomographic studies revealed that oxygen consumption in patients with hypothyroidism is lower than in healthy subjects [103].

Despite these facts, very few clinical studies have addressed the prevalence and clinical significance of cardiac arrhythmias in patients with hypothyroidism. This retrospective age-, gender- and ethnicity-matched case control study revealed a statistically higher prevalence of ventricular arrhythmias in patients with hypothyroidism. Additionally, two patients from the hypothyroid group had ventricular fibrillation. Unfortunately, this dangerous arrhythmia was the cause of their deaths. One of the aims of this study is to shed light on the prevalence of arrhythmias in hypothyroidism. There is a need for future large scale prospective studies to better define the risk factors of ventricular arrhythmias and to evaluate the possible preventive effects of thyroxine supplementation.

Even though, there is a long-recognized link between thyroid dysfunction and cardiovascular risk, and an awareness that thyroid hormones regulate expression of K^+ channels in the heart [103, 104], recent discovery of a crucial role for KCNE2 and KCNQ1 in thyroid hormone biosynthesis presents a novel and unexpected genetic link between thyroid dysfunction and cardiac arrhythmias. Mutations in KCNE2 and KCNQ1 have been associated with long QT syndrome (LQTS), atrial fibrillation, and even early-onset myocardial infarction [105, 106, 107, 108, 109], suggesting the possibility of an endocrine component to some KCNE2- and KCNQ1-associated human cardiac disease [110, 111, 112]. Discovery of a key role of KCNQ1 and KCNE2 in the thyroid hormones biosynthesis may lead in future to use of KCNQ1-KCNE2 modulators to treat thyroid dysfunction. These findings should at least be contemplated in future studies of thyroid-related cardiac disease, its molecular etiology and therapy.

5.1. HYPOTHYROIDISM AND CARDIAC ARRHYTHMIAS

Hypothyroidism is known to be associated with several EKG abnormalities including prolonged QT intervals, QRS interval and bradycardias. Although EKG changes in hypothyroidism are known, still little is known about the clinical significance of these EKG changes. The function of the atrial pacemaker is normal and atrial ectopy is rare, but premature ventricular beats and occasionally ventricular tachycardia may occur [79, 113]. This contrasts with thyrotoxicosis, in which atrial tachyarrhythmias are common and ventricular arrhythmias are rare [3].

5.1.1. QT PROLONGATION

The QT interval reflects traditional electrocardiographic parameter of the duration of ventricular repolarization. The QT dispersion is the interlead variability of QT interval that reflects regional variation in myocardial repolarization. Increased QT dispersion has been linked to malignant ventricular arrhythmias [66, 67]. The underlying mechanism may be decreasing potassium flow (Iks), or an increased sympathetic influence on the autonomic cardiovascular system (elevated catecholamine levels, particularly norepinephrine release from sympathetic nerves) [114, 115].

Increased QT has been found to be associated with an increased prevalence of ventricular arrhythmias and sudden death [72, 73, 74]. Clinical observations show that sudden death is uncommon in hypothyroidism, despite the marked lengthening of the QT interval [75, 76, 77]. However, there was a recently published a case of a 25-year old female with history of severe hypothyroidism, noncompliant with treatment who presented to the hospital after being found unresponsive and pulseless. Paramedics found her being in Ventricular Fibrillation. She received CPR and she was defibrillated twice. ROSC was attained. Her EKG showed sinus bradycardia with QTc of 624 ms, T wave inversion, and low lead voltage. She was promptly begun on intravenous levothyroxine and stress dose steroids. With appropriate treatment, her heart rate improved, QTc normalized to 418 ms, and the lead voltage improved. A genetic analysis done to screen for hereditary long QT syndromes was negative for SCN5A, KCNH2, KCNQ1, KCNE1, KCNE2, and KCNJ2 mutations. She was followed carefully to ensure treatment compliance and no further arrhythmias were documented. It was the first described case of sudden cardiac death due to hypothyroidism [143].

There were studies which showed that QT dispersions improved after the L-thyroxine treatment in patients with primary hypothyroidism [68]. The syndrome of torsade de pointes with a long QT interval and ventricular tachycardia can occur in hypothyroidism and can be resolved with T4 treatment alone [116, 117]. Nathaniel et al. reported that significant prolongation of the QTc interval occurred in inadequately treated hypothyroidism and the

degree of the QTc prolongation were directly related to the severity of hypothyroidism [69]. Altun et al. also showed that QT prolongation and increased QTd were directly related to the TSH levels in hypothyroidism [70]. Kweon et al. studied the effects of levothyroxine supplementation on QT interval and QT dispersion in hypothyroid patients and found that levothyroxine therapy significantly decreased the QT intervals and QT dispersion [78]. This suggests that the thyroid hormone affects ventricular inhomogenicity, and subsequent L-thyroxine replacement therapy may reduce malignant ventricular arrhythmia and sudden cardiac death in patients with hypothyroidism [78]. There was only one study which showed no relationship between TSH or T3 levels and QTc intervals during hypothyroidism, but there was a moderate correlation between lesser degrees of T4 depression and increasing QTc interval [71]. The discrepancy could be explained by a very small number of subjects included in this study.

In my study, I did not evaluate QT intervals, however on a retrospective review of EKG, two patients from the hypothyroid group who had died from ventricular fibrillation, had prolonged QT interval. More studies evaluating QT interval in patients with hypothyroidism may help to define the risk of life-threatening ventricular, prolong survival, and decrease of overall mortality in patients with hypothyroidism.

5.1.2. VENTRICULAR ARRHYTHMIAS

The increased prevalence of ventricular arrhythmias in hypothyroidism could be explained by our current knowledge of the regulatory effects of thyroid hormone on cardiac myocytes. Molecular studies have shown that thyroid hormones regulate cardiac potassium and calcium channels and thereby thyroid dysfunction predisposes to decreased electrical activity of the heart. Microarray analyses in mice models were conducted by Bouter et al. and they have revealed that hypothyroidism induces significant reductions in KCNA5, KCNB1, KCND2, and KCNK2 transcripts, whereas KCNQ1 and KCNE1 expression is increased. They also found that transcripts for the pacemaker channel HCN2 were decreased and for the α1C Ca2+ channel (CaCNA1C) were increased [118]. Another recent study in mice showed that the KCNQ1 and KCNE2 potassium channel genes are also involved in thyroid biosynthesis and that this could be a possible genetic link between prolonged QT syndromes and thyroid dysfunction [119]. Other studies have shown that in rats hypothyroidism reduces the transient outward current (Ito) density [120].

In my study, any ventricular arrhythmia occurred more frequently in the hypothyroid group than in the control group and it was statistically significant (10 patients vs 2 patients respectively, p=0.02). Nonsustained ventricular tachyarrhythmia (NSVT) was twice more common in hypothyroid patients (4 patients) than in euthyroid patients (2 patients), but it was not statistically significant (p=0.41). Ventricular fibrillation (VF) was observed in two patients from the hypothyroid group and in none of the patients from the control group. The difference was not statistically significant with p-value 0.15. Unfortunately, both patients died, despite performing aggressive resuscitation measurement. It is important to add that both patients were females (56 and 80 years old) who were admitted only for syncope, none of them had significant past cardiac history. TSH level was 69.42 μIU/mL and 45.68 μIU/mL respectably. They did not have systolic or diastolic congestive heart failure and no history of previous hospitalizations for any arrhythmia or other cardiac issues. Retrospective review of these patients EKG showed prolonged QT interval. Unfortunately, there was no previous EKG available to compare.

Also, idioventricular rhythm was recorded on a telemetry monitor in one patient with hypothyroidism and in none of the patients with normal thyroid function, however it was not statistically significant ($p=0.31$).

Osborn et al. studied ten hypothyroid patients before and after L-thyroxine therapy and reported that hypothyroidism is not associated with clinically significant ventricular tachyarrhythmias [71]. These results contradict the findings of my current study. The discrepancy could be explained in terms of the differences in study design, mine is a retrospective case control study involving a substantially larger number of subjects while Osborn et al. studied the effects of thyroid supplementation on ventricular ectopy in a small number of subjects, over a very short length of time. Because of the differences in study groups and the design of the studies, I believe that the results of both studies are valid, but not in direct comparison due to many incompatible variables.

5.1.3. ATRIAL FUNCTION

Measurement of the left atrial (LA) size is the most commonly used method to estimate the amount of atrial remodeling. LA volumes and LA mechanical functions have recently been identified as potential indicators of cardiac disease and arrhythmias [121, 122, 123]. Intraatrial conduction delay and non-homogenous propagation of sinus impulses are well known electrophysiological distinctiveness of the atria prone to fibrillation [124]. Contrary of LA size, atrial conduction times reflect the amount of both electrical and structural remodeling of the atria. Recently, it has been shown that rheumatoid arthritis, paroxysmal atrial fibrillation and systemic lupus erythematous may impair LA functions and atrial conduction time [124, 125, 126]. However, LA mechanical functions and atrial conduction abnormalities in patients with hypothyroidism have not been fully investigated.

The left atrium has three distinct mechanical functions: reservoir, passive emptying and active emptying which all happen at different stages of the cardiac cycle. The reservoir function takes effect during ventricular systole, the passive emptying function occurs in early diastole and the active emptying function occurs during ventricular diastole. If left ventricular dysfunction occurs, the left atrium may possibly preserve adequate cardiac output by regulation of reservoir and booster pump functions. These effects are more prevalent in patients with reduced left ventricular (LV) function [81, 82]. Hereby, impaired LA function may result in the development of heart failure in patients with hypothyroidism [127].

Ozturk et al. performed a prospective study to explore electromechanical changes in atrial function in hypothyroid patients and it demonstrated that the left atrium (LA) mechanical functions were significantly impaired in patients with hypothyroidism. LA passive emptying volume and LA passive emptying fraction were also significantly decreased but the LA active emptying volume and LA active emptying fraction were significantly increased in hypothyroidism patients [80]. These parameters also positively correlated with the TSH and negatively correlated with T4 levels. They concluded that these changes might be related to the increased risk of cardiac arrhythmias [80].

My study did not find any increases of occurrence of atrial arrhythmias in patients with hypothyroidism. There was not difference in the prevalence of any supraventricular tachycardia (SVT) between both groups (28 vs 30 patients, p=0.77). Atrial fibrillation was diagnosed in 21 patients in the hypothyroid group and in 20 patients in the euthyroid group (p=0.86). Junctional rhythm was present almost twice as often in patients with hypothyroidism than in patients with normal thyroid function. There were 11 patients with junctional rhythm in Group 1 and only 6 patients in the control group, however it was not statistically significant (p=0.2). Atrial flutter was almost twice more often in the control group than in the study group, but it was not statistically significant (7 vs 4 patients respectively, p=0.35).

5.1.4. PR INTERVAL AND QRS DURATION

Very few studies have evaluated the association of thyroid hormone levels with electrocardiographic parameters such as PR interval or QRS duration. Experimental studies in hypothyroid dogs did show prolonged P wave and QRS duration compared to euthyroid dogs [128]. In humans, however, a study of 18 patients with hypothyroidism, found no significant changes in the PR and QRS duration after L-thyroxine treatment [78]. Additional studies are needed to confirm these observations.

5.2. GENETIC LINK OF CARDIAC ARRHYTHMIAS AND HYPOTHYROIDISM

Inherited long QT syndrome, a cardiac arrhythmia that often predisposes individuals to the life-threatening ventricular fibrillation, is commonly linked to mutations in potassium voltage-gated channel subfamily Q member 1 (KCNQ1). The KCNQ1 voltage-gated K^+ channel α subunit passes ventricular myocyte K^+ current that helps bring a timely end to each heartbeat. KNCQ1, like many K^+ channel α subunits, is regulated by KCNE β subunit. It is also known that inherited mutations in KCNQ β subunit are associated with long QT syndrome. KNCQ1 and KCNE mutations are also associated with atrial fibrillation [106, 119]. Purtell et al. recently discovered that KCNQ1and KCNE2 form a thyroid-stimulating hormone K^+ channel in the thyroid. This channel is required for normal thyroid hormone biosynthesis. Because the heart is strongly influenced by the thyroid, these finding suggests that these two K^+ channel subunits may influence cardiac function, directly due to their roles in cardiac myocytes, and indirectly, by their role in thyroid physiology.

Excitable cells facilitate dynamic process such as rhythmic beating of the heart. Excitability, defined by the heart's ability to sustain action potentials, requires voltage-gated sodium (Na_V) channels for the depolarization phase (upstroke) and voltage-gated potassium (K_V) channels for the repolarization phase (downstroke) (Figure 48A). The ventricles of the human heart provide most of the contractile force for pumping blood around the body and the integrity of ventricular myocyte action potentials are crucial for life. Influx of Na^+ ions through Na_V depolarizes human ventricular myocytes, and K^+ efflux through a variety of K^+ channel types, primary K_V channels, facilitates myocyte repolarization. The most prominent repolarization phase, Phase 3, is coordinated primarily by two K_V α subunits: hERG and KCNQ1, which respectively generate the I_{Kr} and I_{Ks} repolarization currents (Figure 48 B). The cumulation of ventricular repolarization manifests on electrocardiogram at the end of the T wave (Figure 48 C) [119].

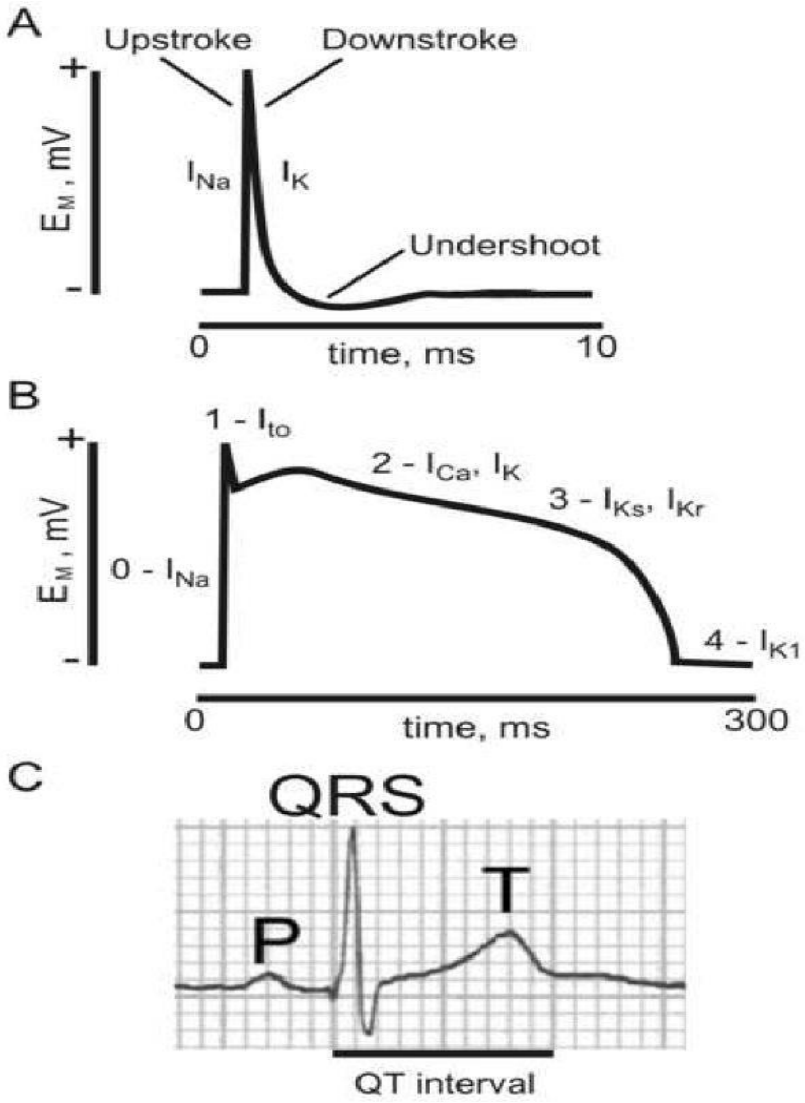

FIGURE 47 - Action potentials and the surface electrocardiogram. Purtell K, Roepke T, Abbott G. Cardiac arrhythmia and thyroid dysfunction: a novel genetic link. *Int J Biochem Cell Biol.* 2010; 42:1767-1770 (modified) [119].

A. Neuronal action potential **B**. Ventricular myocyte action potential. Phases 0-4 are indicated, with prominent currents during these phases. **C**. EKG showing P and T waves, QRS complex, and QT interval **Abbreviations**: I_{Na}, sodium current; I_K, potassium current; E_M, membrane potential; I_{to}, transient outward K_V current; I_{Ca}, voltage-gated calcium current; I_{Ks}, slowly activating K^+ current; I_{Kr}, rapidly activating K^+ current; I_{K1}, inward rectifier K^+ current

KCNQ1 and hERG contain six transmembrane helices within which is a voltage sensor that moves up membrane depolarization and then opens to permit ion flux. In vivo, hERG and KCNQ1 each form complexes with KCNE β subunits, also referred to as MinK-related peptides (MiRPs). KCNE subunits are single-transmembrane-segment (TMS) proteins that do not pass current alone, but co-assemble with pore-forming K_V α subunits to regulate their trafficking, gating, conductance, regulation by other proteins, and pharmacology (Figure 49) [119]. Importantly, both KCNE β subunits and K_V α subunits are promiscuous, helping to create K^+ current diversity but also hampering efforts to determine molecular correlation of native currents. Thus, the KCNQ1-KCNE1 channel activates more slowly and at more positive membrane potentials than homomeric KCNQ1, and generates the I_{Ks} human ventricular repolarization current (with possible contributions from other KCNQ1-KCNE complexes) [119]. KCNQ1 has a property unique among K_V α subunits, it can be converted to a constitutively open K^+ leak channel (e.g. does not require membrane depolarization to open) by co-assembly with the KCNE2 or KCNE3 ancillary subunits [112, 129]. It is still not yet known whether KCNQ1 form leak channels in human heart with KCNE2 or KCNE3, the ability to open constitutively has been shown to facilitate functional roles for KCNQ1-KCNE complexes in non-excitable, polarized epithelia in vivo. Recent studies discovered that KCNQ1 and KCNE2 form a constitutively-active- K^+ channel in thyrocytes, and that the KCNQ1-KCNE2 channel is required for normal thyroid hormone biosynthesis [129].

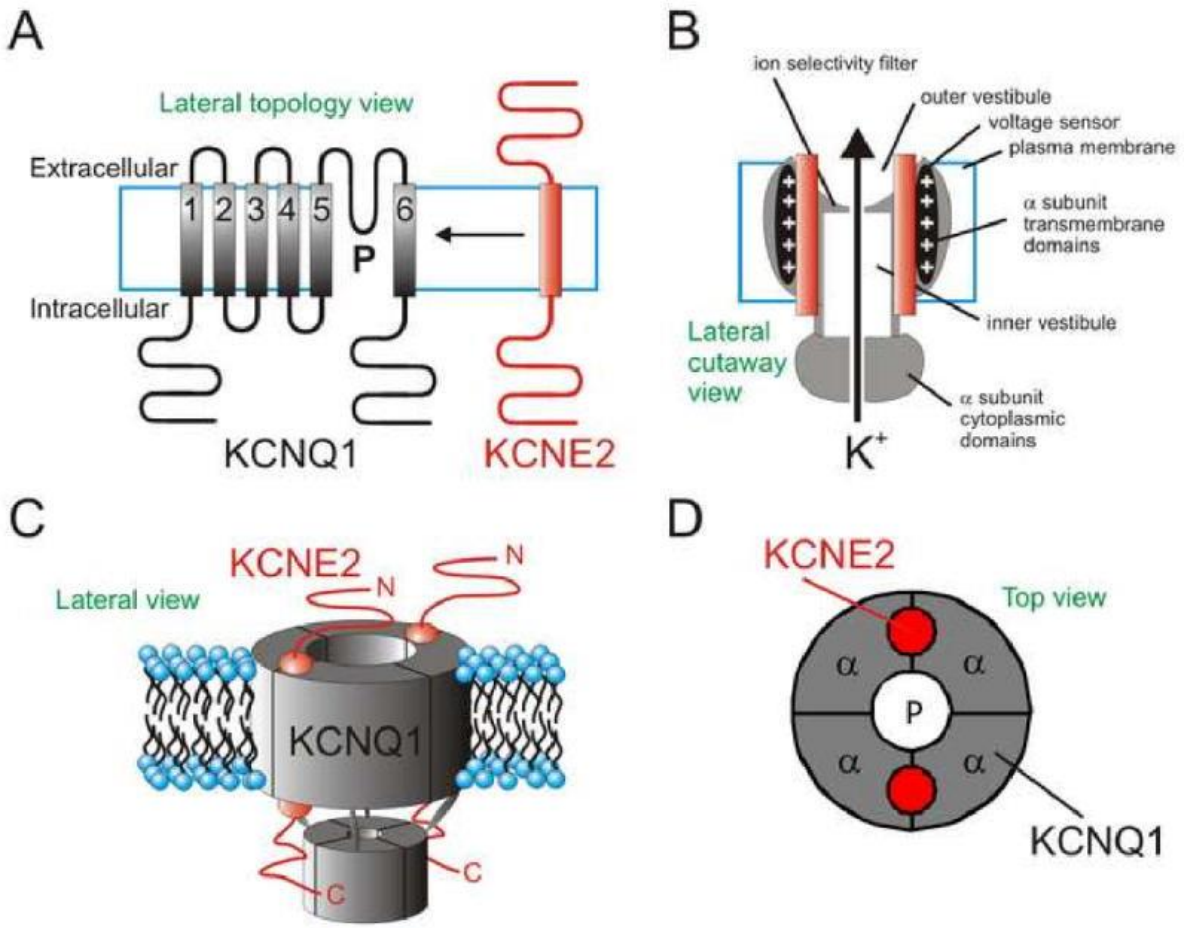

FIGURE 48 - - KCNE2 and KCNQ1. Purtell K, Roepke T, Abbott G. Cardiac arrhythmia and thyroid dysfunction: a novel genetic link. *Int J Biochem Cell biol*. 2010; 42:1767-1770 (modified) [119].

A. Topology of KCNQ1 and KCNE2 in cell membrane **B.** Lateral view of KCNQ1-KCNE2 complex (KCNQ1, grey; KCNE2, red) **C.** Cartoon lateral view of a KCNQ1-KCNE2 channel complex **D.** Cartoon top view of a KCNQ1-KCNE2 complex suggesting a possible juxtaposition of two subunit types

Purtell et al. identified that KCNE2 mutations are associated with inherited long QT syndrome (LQTS). The presumed mechanism is a disruption of ventricular myocyte hERG-KCNE2 channels [107]. KCNE2 has also been found to regulate I_{Kr} *in vivo* in canine ventricles [130] and mouse sinoatrial node [110]. Roepke et al discovered that 3-month-old *Kcne2*$^{-/-}$ mice have impaired ventricular myocyte repolarization due to loss of KCNE2 from myocyte channel complexes (K_V4.2 and K_V1.5 α subunits) [111]. Breeding of *Kcne2*$^{-/-}$ dams results in hypothyroidism in both the pregnant dams and their pups, due to a previously unreported role for the KCNQ1-KCNE2 K^+ channel in thyrocytes [131]. *Kcne2*$^{-/-}$ mice born to *Kcne2*$^{-/-}$ dams, by 3 weeks of age, show marked cardiac abnormalities including cardiomegaly, hypertrophy and impaired contractility. These mice also exhibit alopecia, defective skeletal development, 50% embryonic lethality, and delayed growth resulting in dwarfism [131]. All these symptoms are also observed in human congenital hypothyroidism [132]. *Kcne2*$^{-/-}$ pups born to *Kcne2*$^{+/-}$ dams, at the beginning they appear to develop normally, and by three months are euthyroid (indicating a strong influence of maternal genotype on phenotype), they exhibit latent hypothyroidism with cardiomegaly, alopecia, diminished T_4 and elevated TSH levels by 1 year of age [131]. As previously observed in hypothyroid rats, *Kcne2*$^{-/-}$ dams have impaired milk ejection - alleviated by oxytocin injection - partially explaining the influence of maternal genotype in *Kcne2*$^{-/-}$ mouse phenotype severity [131, 133].

The Na^+/I^- symporter (NIS) is responsible for the accumulation of I^- in thyrocytes in the first step of thyroid hormones biosynthesis. I^- is then transported apically into the colloid in the thyroid lumen where it is organified into thyroglobulin (Tg) and subsequently incorporated into T_3 and T_4. NIS uses Na^+ movement to accumulate I^- into thyrocytes. While it has previously been established that the Na^+/K^+ATPase, which co-localizes with NIS at the basolateral membrane, generates this gradient by pumping Na^+ out in exchange for moving K^+ in [134], the pathway responsible for moving K^+ back out of the cell has remained enigmatic. Purtell et al. recent findings show that KCNE2, probably primarily in complexes with KCNQ1, is required for normal I^- accumulation in the thyroid, suggesting that the KCNQ1-KCNE2 channel may form the thyrocyte K^+ efflux pathway [119].

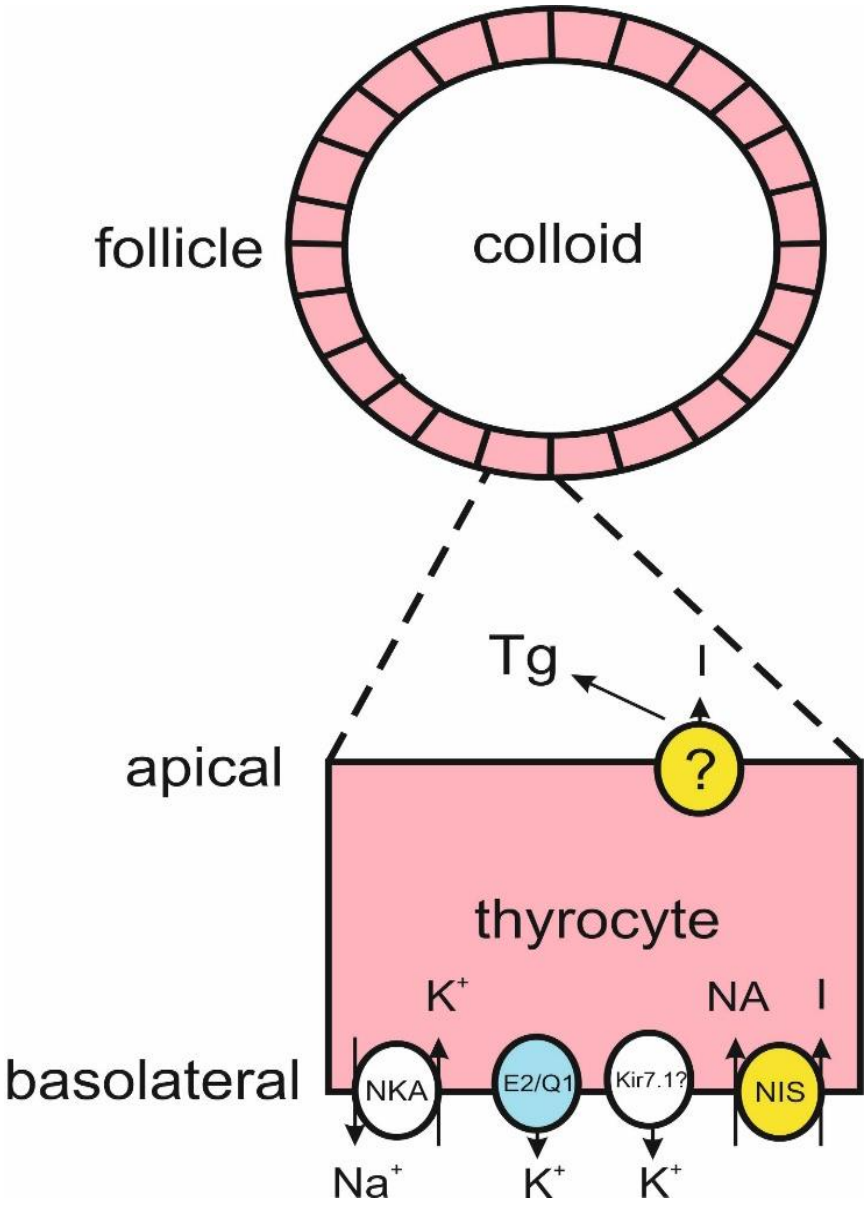

FIGURE 49 - KCNQ1-KCNE2 channel. Purtell K, Roepke T, Abbott G. Cardiac arrhythmia and thyroid dysfunction: a novel genetic link. *Int J Biochem Cell biol*. 2010; 42:1767-1770 (modified) [119].

Putative role for KCNQ1-KCNE2 (blue) in thyrocytes is to facilitate K^+ efflux basolaterally. A subset of other channels and transporters are shown for context: Kir7.1, inward rectifier K^+ channel; NKA, Na^+/K^+/ATPase; NIS, Na^+/I^- symporter (yellow). At the apical membrane, I^- passes from the thyrocyte to the colloid for organification, through pendrin or another, unspecified protein (yellow), resulting in formation of thyroglobulin (Tg).

In summary, the KCNQ1-KCNE2 K^+ channel appears to be an important factor for the normal thyroid hormones biosynthesis in mice. KCNQ1 and KCNE2 are also expressed in human thyroid, but we still do not know their entire function there, or the consequences of their disruption on the thyroid cells. A possible role for thyroid dysfunction in KCNQ1- and KCNE2-associated cardiac arrhythmias and myocardial infarction warrants consideration in future anti-arrhythmic regimes involving pharmacologic modulation of KCNQ1.

I think this recent discovery of this novel genetic link between cardiac and thyroid physiology and pathology is a great start for further genetic studies. This molecular background may help in future therapeutic strategies, not only in thyroid diseases, but also cardiac dysfunction.

It is worth to mention that the control group included patients who were admitted to the hospital for cardiac reasons like chest pain, myocardial infarct, unstable angina, syncope, congestive heart failure exacerbation, atrial fibrillation, cardiomyopathy. There is a chance that if subjects were selected from population who were not recently hospitalized, I would find more statistically significant differences in cardiac arrhythmias between hypothyroid and euthyroid patients.

Limitations to the current study include its retrospective nature, limited number of patients, fact that hypothyroidism was diagnosed based on one measurement of TSH and fT4 level with unknown etiology of hypothyroidism and the inability to monitor for arrhythmia episodes after being released from the hospital.

6. SUMMARY AND CONCLUSIONS

This retrospective age-, gender- and ethnicity-matched case control study revealed:

1. A statistically higher incidence of any ventricular arrhythmias in patients with hypothyroidism.
2. A statistically higher prevalence of ventricular tachycardia.
3. Ventricular fibrillation was documented in two patients from the hypothyroid group and in none of the patients from control group, however it was no statistically significant.
4. Both patients with ventricular fibrillation from the hypothyroid group died, despite performing aggressive resuscitation measurement.
5. Junctional rhythm and intraventricular rhythm were noticed more frequently in the hypothyroid group than in patients with normal thyroid function, however it was not statistically significant.
6. There was no difference in occurrence of atrial arrhythmias in patients with hypothyroidism and in the euthyroid group.

CONCLUSIONS:

1) The present study has shown higher prevalence of any ventricular arrhythmias and ventricular tachycardia. This has shed light on the prevalence of arrhythmias in patients with hypothyroidism and the need for further studies.

2) There were two lethal cases due to ventricular fibrillation in the hypothyroid group. These particular patients may need more intensive preventive care for arrhythmias than the general population.

3) Limitations to the current study include its retrospective nature, limited number of patients, fact that hypothyroidism was diagnosed based on one measurement of TSH and fT4 level with unknown etiology of hypothyroidism and the inability to monitor for arrhythmia episodes after being released from the hospital.

4) There is a need for future large scale prospective studies to better define the risk factors of ventricular arrhythmias and to evaluate the possible preventive effects of thyroxine supplementation.

7. ABSTRACT

Thyroid hormones affect various functions of the heart including contractility and chronotropic functions of the heart. The association of hyperthyroidism with atrial tachyarrhythmias is well established but only few clinical studies have addressed association of hypothyroidism and cardiac arrhythmias. Though EKG changes in hypothyroidism, including prolongation of QT interval, QRS interval and bradycardias, are known, still very little is known about the clinical significance of these EKG changes. This retrospective case control study was conducted to analyze differences, if any, in the prevalence of cardiac arrhythmias between hypothyroid patients and euthyroid controls, and to establish clinical significance of cardiac arrhythmias in hypothyroid patients.

A total of 304 consecutive patients admitted to the Cardiology floor at Albert Einstein Medical Center in Philadelphia. Pennsylvania, United States of America between June 2011 and May 2012 were included in the study. Based on the TSH level the study population was divided into two groups: patients with hypothyroidism and euthyroid subjects as a control group. Major arrhythmia data (tachyarrhythmias: atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular node reentrant tachycardia, ventricular tachycardia, nonsustained ventricular tachycardia, ventricular fibrillation, and bradyarrhythmias: sinus bradycardia, atrioventricular block, junctional rhythm, idioventricular rhythm) were obtained from the EKG, chart documentation of known past medical history and from telemetry recording. Left ventricular systolic and diastolic function were evaluated based on transthoracic echocardiogram result, chest x-ray, physical exam and elevated B-type natriuretic peptide (BNP) level. Patients were divided into 4 categories: any congestive heart failure (systolic and/or diastolic), systolic heart failure (EF<50%), diastolic heart failure and patients with normal ejection fraction.

There were 152 (age-, gender- and ethnicity-matched) subjects in each arm of the study.

Mean age in the hypothyroid group was 61.9± 19.2 years old and 61.9 ± 19.2 years old in the euthyroid group. Mean TSH in hypothyroid group was 40.4 ± 44.68 μIU/mL (95 % CI 33.3-47.5) and 0.89 ± 0.43 μIU/mL (95 % CI 0.82-0.96) in the hypothyroid group.

Chi-square analysis revealed a higher prevalence of ventricular tachycardia (P-value 0.04) and any ventricular arrhythmia in the hypothyroid group (p-value 0.02). Unfortunately, both patients with ventricular fibrillation from the hypothyroid group died, despite performing aggressive resuscitation measurement.

This case control study revealed a statistically higher occurrence of ventricular arrhythmias in hypothyroidism. My study has thrown light on the prevalence of arrhythmias in hypothyroidism and the observation of increased ventricular arrhythmias necessitates future large scale prospective studies to better define the risk of such ventricular arrhythmias and the effects of thyroid supplementation on this risk. Identifying the life-threatening arrhythmias in patients with hypothyroidism can help to detect heart disease earlier, prolong survival, and decrease overall mortality in this group of patients. These patients may need more intensive preventive care for arrhythmias than general population. Limitations to the current study include its retrospective nature, fact that hypothyroidism was diagnosed based on one measurement of TSH and fT4 level with unknown etiology of hypothyroidism and the inability to monitor for arrhythmia episodes after being released from the hospital.

8. STRESZCZENIE

Hormony tarczycy mają różnorodny wpływ na funkcję pracy serca, jednak najważniejsze z nich to ich inotropowy i chronotropowy efekt. Zależność pomiędzy nadczynnością tarczycy a przedsionkowymi tachyarytmiami jest już szeroko omówiona w literaturze przedmiotu, natomiast bardzo niewiele badań klinicznych poświęcono zagadnieniu zależności pomiędzy niedoczynnością tarczycy a zaburzeniami rytmu serca. Zmiany w zapisie EKG, takie jak zespół wydłużonego odstępu QT, zespół wydłużonego zespołu QRS oraz bradykardie zostały odnotowane u osób z niedoczynnością tarczycy, ale wciąż niewiele jest wiadomo na temat klinicznych skutków, jakie wywierają one na pacjenta.

Celem mojego retrospektywnego badania było zbadanie różnicy w częstotliwości występowania zaburzeń rytmu serca pomiędzy pacjentami z niedoczynnością tarczycy a pacjentami z prawidłową czynnością tarczycy, oraz ustalenie klinicznych następstw tych arytmii u pacjentów z niedoczynnością tarczycy.

Do badania zostało zakwalifikowanych trzystu czterech pacjentów hospitalizowanych w okresie od czerwca 2011 do maja 2012 na Oddziale Kardiologii w szpitalu Albert Einstein Medical Center w Filadelfii w Stanach Zjednoczonych. Na podstawie badania podmiotowego i przedmiotowego oraz oceny stężenia hormonu TSH zostali oni podzieleni na dwie grupy: pacjentów z niedoczynnością tarczycy oraz pacjentów z prawidłową funkcją tarczycy (jako grupa kontrolna). Zaburzenia rytmu serca, takie jak migotanie przedsionków, trzepotanie przedsionków, częstoskurcz zatokowy, częstoskurcz nawrotny w węźle przedsionkowo-komorowym, częstoskurcz komorowy, migotanie komór, bradykardia, blok przedsionkowo-komorowy oraz pozazatokowe zaburzenia nadkomorowe w obu badanych grupach zostały zebrane na podstawie zapisu EKG, dokumentacji medycznej pacjentów oraz zapisu telemetrii. Na podstawie badania echokardiograficznego, badania rentgenowskiego klatki

piersiowej, podwyższonego poziomu peptydu natiuretycznego BNP oraz badania fizykalnego badani zostali podzieleni na cztery grupy. Pierwsza- z jakąkolwiek niewydolnością serca (skurczową lub rozkurczową), druga- ze skurczową niewydolnością serca (frakcja wyrzutowa <50%), trzecia-z rozkurczową niewydolnością serca oraz czwarta-z prawidłową pracą serca.

Średnia wieku w grupie pacjentów z niedoczynnością tarczycy wynosiła 61.9 ± 19.2 lat i 61.9 ± 19.2 lat w grupie kontrolnej. Średnie stężenie TSH w grupie pacjentów z niedoczynnością tarczycy wynosiło 40.4 ± 44.68 μIU/mL (95 % CI 33.3-47.5), a w grupie kontrolnej 0.89 ± 0.43 μIU/mL (95 % CI 0.82-0.96). Test Chi-square wykazał wyższą częstotliwość występowania częstoskurczu komorowego (p-value 0.04) oraz arytmii komorowych (p-value 0.02) u pacjentów z niedoczynnością tarczycy. Dwóch pacjentów z niedoczynnością tarczycy, zdiagnozowanych z migotaniem komór, pomimo przeprowadzonej agresywnej akcji reanimacyjnej, zmarło na skutek tej arytmii.

Założeniem mojego badania było przedstawienie problemu arytmii i ich klinicznych skutków u pacjentów z niedoczynnością tarczycy, a to relatywnie duże badanie wykazało statystycznie istotne częstsze występowanie komorowych zaburzeń rytmu serca u osób z niedoczynnością tarczycy. Mój elaborat potwierdził konieczność prowadzenia kolejnych badań nad czynnikami ryzyka komorowych zaburzeń serca, a także nad leczeniem suplementacyjnym hormonami tarczycy, które mogłoby to ryzyko obniżyć lub wyeliminować. Znajomość owych czynników ryzyka arytmii może ułatwić szybsze diagnozowanie chorób układu naczyniowo- krążeniowego, wydłużyć przeżywalność, a także obniżyć śmiertelność u pacjentów z niedoczynnością tarczycy. Ta szczególna grupa pacjentów może potrzebować intensywniejszych działań prewencyjnych niż ogólna populacja.

W tym miejscu należy nadmienić, iż ograniczeniami mojej pracy był jej retrospektywny charakter, fakt, że niedoczynność tarczycy była zdiagnozowana na podstawie jednego pomiaru TSH i fT4 bez znajomości etiologii niedoczynności oraz brak możliwości monitorowania zaburzeń rytmu serca u pacjentów po ich wypisaniu ze szpitala.

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10. INDEX OF FIGURES

11. INDEX OF TABLES