

Manuscript ID
DOIZUMJ-1909-1555 (R1)
10.21608/zumj.2020.17510.1555**ORIGINAL ARTICLE****Assessment Of Thyroid Functions in Infants and Children with Heart Failure Due to Congenital Heart Disease**⁽¹⁾ Eman Mahmoud El-Moghazy ⁽¹⁾ Al-Shaymaa Ahmed Ali ⁽²⁾ Hanan Samir Ahmed, and ⁽¹⁾ Samar Omar Mohamed

Department of (1)Pediatrics, (2)Clinical pathology Faculty of Medicine – Zagazig University, Egypt.

Corresponding author

Samar Omar Mohamed.

E.mail :

samaromar858@gmail.com**Submit Date** 2019-10-02
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Accept Date 2020-04-22**ABSTRACT****Background:** Euthyroid Sick Syndrome is a common endocrinal change following any acute or chronic illness like those with heart failure. This study aimed to explore that thyroid function may be altered in patients of heart failure and this may affect the severity and outcome of heart failure.**Methods:** This case-control study was conducted in Pediatric cardiology unit, Pediatric department, Zagazig University Hospitals from April 2018 to January 2019. This study included 84 infants and children, divided into 2 groups, 42 patients with heart failure due to congenital heart disease in comparison to other 42 healthy infants and children.**Results:** In our study we revealed that FT3 and FT4 were significantly lower among studied cases than their controls and TSH was higher among cases. In ECHO findings, the mean of EF% and FS% was lower among studied cases with positive correlation of FT3, FT4 with EF% and FS%, while TSH showed a negative correlation with EF and FS. Also our study showed that there was statistically significant relation between all thyroid functions and Ross classification for severity of heart failure, it was found that the mean of FT3 and FT4 in grade IV was lower than that of grade II and III, While the mean of TSH was higher in grade IV than grade II, III.**Conclusions:** our study, thyroid function can be altered in pediatric heart failure and this alteration in thyroid function may be related to the severity of heart failure and worse outcome.**Keywords:** Thyroid Functions , Heart Failure , Heart Disease , Cardiac failure.**INTRODUCTION**

Cardiac failure is a clinical syndrome where the heart is unable to provide the output required to meet the metabolic demands of the body at normal physiologic venous pressures, the heart can respond to increased demands by increasing heart rate, increasing the contractility of the ventricles or augmenting the preload by constricting the venous capacitance vessels [1].

Pediatric heart failure (PHF) is now being increasingly recognized as an important source of health care resources utilization with 11,000 to 14,000 heart failure related hospital admission in the United States every year[2]. The causes and mechanisms of cardiac failure are significantly different between adults and pediatrics. In infants

and children, the most common causes are due to congenital malformations [3].

The yearly incidence of congenital defects in the United States is between 1 and 2 per 1000 live births [4]. Euthyroid sick syndrome is a term used to define a condition characterized by an impairment of the hypothalamus–pituitary–thyroid axis present in most critically ill patients like those with heart failure with non thyroidal illness. A fall in serum triiodothyronine (T3), also known as low T3 syndrome, is one of the most common changes observed[5]. As Thyroid hormones have cardiac and vascular effects, and they also regulate biochemical reactions in most tissues. Altered thyroid hormone metabolism, characterized by low circulating levels of biologically active

triiodothyronine (T3), has been reported in patients with congestive heart failure[6]. The progressive decrease in triiodothyronine levels, may be part of the pathologic processes leading to a progressive disturbance of the cardiovascular system, as it was found that low T3 levels in HF patients is associated with several markers of illness that lowers anabolic activity and cause more severe membrane damage, this could partially explain a more advanced HF status among patients with low T3 levels[7]. So, Thyroid function tests may be particularly helpful for assessing the severity and prognosis of heart failure[8].

Many studies have been done in adults admitted to coronary care unit to prove altered thyroid products in heart failure and that low T3 is an independent predictor of death in cardiac patients and this may affect prognosis and severity of heart failure [9], [10],[11]. But few studies have been done in pediatrics for evaluation of thyroid function in heart failure [12].

Novitzky and colleagues performed two smaller randomised studies in 2016 using T3 supplementation and showed a significantly reduced need for conventional inotropic agents and diuretics as well as improved stroke volume, cardiac output, reduced systemic and pulmonary vascular resistances and survival [13]. This study aimed to assess thyroid function in infants and children with heart failure due to congenital heart disease and to correlate this with the severity of heart failure.

PATIENTS AND METHODS

This case-control study was conducted in Pediatric cardiology unit, Zagazig University Hospitals from April 2018 to January 2019. This study was conducted on 42 patients with heart failure due to congenital heart diseases (Group 1= Case group) as we ruled out other causes of heart failure, compared with other 42 healthy infants and children (Group 2= Control group) with no significant difference between cases and controls in age and gender, so they were comparable groups. Echocardiographic exams were performed by the same operator using a Vivid 7 dimension (General Electric) machine equipped with a multi-frequency matrix M3S and a 7s transducers and Zaouti My Lab five simultaneous ECG recording.

Inclusion criteria: Patients with heart failure due to congenital heart disease either cyanotic or non cyanotic, acute or chronic. Patients age from one month up to 5 years old. Ability to provide informed consent from the caregiver. **Exclusion criteria:** Patients with clinical evidence of sepsis, cachexia, or other severe systemic disease. Patients with known altered thyroid function

hypothyroidism or hyperthyroidism. Patients refuse to sign consent. Patients age more than 5 years old and less than 1 month.

Ethical Clearance: Written Informed consent was taken from the patient parents to participate in the study. Approval for performing the study was obtained from Pediatrics and Clinical Pathology Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. The work was carried out for human studies in accordance with the World Medical Association's Code of Ethics (Helsinki Declaration).

Methods: All patients included in this study were subjected to: Complete history taking through a standardized clinical cardiology sheet with special emphasis on Name, age, sex, weight, duration of illness and improvement if rapid or delayed according to the duration of stay in the hospital considering rapid if the duration is less than 1 week and delayed if more than 1 week. Symptoms of heart failure. Presence of cyanosis and its onset. Anti-failure drugs received (number, types, doses and duration).

All patients received angiotensin converting enzyme (Capotril) and Furosemide. Dobutamine was added to some patient with severe heart failure. Digitalis was given to patients with reduced ejection fraction.

According to the history taken the patient were classified according to the symptom based on Modified Ross classification of heart failure [14].

General and local examination: Anthropometric measurement including weight, length or height, and body mass index (BMI) by the equation of: $BMI(Kg/m^2) = Weight (Kg) / (length(m)^2)$.

General examination including vital signs (H.R., R.R., B.P., temperature), edema, cyanosis and clubbing. Heart rate and Respiratory rate assessment: were calculated over one minute. Local examination of the heart. Inspection and palpation for pulsation, pericardial bulging, retractions and thrill. Auscultation of heart sounds, murmurs either systolic or diastolic and additional sounds as s3 gallop.

Echocardiography(TTE): Echocardiographic exams were performed with all subjects positioned in supine decubitus and left lateral decubitus with sedation if required using oral chloral hydrate. Echocardiographic exams were performed by the same operator using a Vivid 7 dimension (General Electric) machine equipped with a multi-frequency matrix M3S and a 7s transducers and Zaouti My Lab five simultaneous ECG recording at The Echocardiography Laboratory of Children's Hospital, Zagazig University.

Initially, routine diagnostic imaging was performed, including colour flow mapping, pulsed, and continuous wave Doppler. Colour Doppler myocardial imaging was performed with a standard apical four-chamber view. Sector size and depth were chosen to achieve a frame rate of 130 ± 20 . Gain settings, filters, and pulse repetition frequency were adjusted to optimize colour saturation, and continuous 1-channel electrocardiographic monitoring was used throughout the study. Three consecutive cardiac cycles were recorded during normal quiet respiration. Data were stored. The studies were video-recorded for subsequent analysis.

Cardiac Dimensions: Echocardiographic measurement was carried out according to the recommendation of the American Society of Echocardiography[15].

Aortic (AO) and left atrial (LA) dimensions were measured from the parasternal short axis view. The main pulmonary artery right & left pulmonary branches were measured from the parasternal short axis view with tilting the plane of the ultrasonic waves toward the base of the heart with slight cranial & leftward angulation of the transducer. Interventricular septum (IVS), left ventricular posterior wall (LVPW) thickness, left ventricular end diastolic (LVED) and left ventricular end systolic (LVES) dimensions were measured from the parasternal short axis view with orientation of the plane of sound just below the tips of the mitral valve. Left ventricular dimensions were measured using the conventional approach: the left ventricular end diastolic diameter was measured at the start of the QRS complex and the end-systolic diameter, in late systole at the time of maximum contraction of the left ventricular posterior wall. The right ventricular end-diastolic diameter (RVEDD) was measured in millimeters and corrected for body surface area measured from the parasternal short axis view.

Conventional LV systolic functions: The left ventricular end diastolic (LVED) and left ventricular end systolic (LVES) dimensions parameters were measured from M-mode (MM) images. The EF and %FS were calculated through M- Mode. [16] **Figure 1.**

Conventional LV diastolic functions: The left

ventricular mitral and tricuspid valve diastolic flow was recorded from apical four-chamber windows as described by **Rakowski et al., [17]** with a 3-5 mm pulsed-sample Doppler volume placed between the tips of the valves. Mitral inflow measurements (at end expiration) included peak early velocity (E), peak late velocity (A), E/A ratio. Parameters were recorded for three consecutive cardiac cycles, and results were averaged. Pulsed Doppler signals were recorded at a horizontal sweep of 100 mm/s[18]. **Figure 2**

Statistical analysis

Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for windows (NCSS LCC., Kaysville, UT, USA). Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage.

RESULTS

Table (1) showed that a statistical significant decrease of E and E/A of mitral valve and significant increase of A among cases as compared to controls reflecting the impaired diastolic functions in cases. Lower systolic functions in cases as compared to controls as the mean of EF and FS was lower among cases. While the mean of pulmonary pressure was higher in cases compared to controls.

Table (2) showed that a high statistically significant difference between studied cases and control groups regarding FT3, FT4 and TSH, as both FT3 and FT4 were significantly lower while TSH was significantly higher in studied cases.

Table (3) showed that there was statistically significant correlation between all thyroid functions and systolic LV functions of studied cases. There was a positive correlation between FT3 and FT4 with EF, FS. While TSH showed a negative correlation with EF and FS.

Table (4), showed that there was statistically significant relation between all thyroid functions and ROSS classification for severity of HF.

Table (5), there was a high statistically significant decrease in FT3 level among patients with acute HF than those with chronic HF, while no significant difference regarding T4 and TSH levels. That FT3 was found to be lower in cases who died as compared to those who survived.

Table (1): (Diastolic , Systolic) functions among cases and controls:

Variables		Cases (N = 42)	Controls (N = 42)	t-test	P value
Diastolic					
E mitral valve (m/sec)	Mean \pm SD Range	0.73 \pm 0.13 0.4 – 1.17	0.88 \pm 0.22 0.64 – 1.6	3.59	0.001 S

Variables		Cases (N = 42)	Controls (N = 42)	t-test	P value
A mitral (m/sec)	Mean ± SD	0.99 ± 0.65	0.73 ± 0.202	MW	0.034 S
	Median	0.75	0.72		
	Range	0.32 – 2.7	0.34 – 1.3		
E/A mitral	Mean ± SD	0.83 ± 0.13	1.27 ± 0.103	9.93	<0.001 HS
	Range	0.61 – 1.2	1.1 – 1.48		
Systolic					
EF	Mean ± SD	52.3 ± 11.02	78.95 ± 6.4	8.1	<0.001 HS
	Range	20 – 62	70 – 89		
FS	Mean ± SD	33.2 ± 8.9	46.3 ± 6.2	7.72	<0.001 HS
	Range	12 – 48	38 – 55		
Systolic Pulmonary pressure	Mean ± SD	54.6 ± 20.6	24.7 ± 4.5	MW	<0.001 HS
	Median	50.0	25.0		
	Range	25 – 100	18 – 32		

S: P-value<0.05 is significant

HS: P-value<0.001 is high significant

EF: Ejection Fraction

FS: Fraction Systolic

Table (2): Thyroid functions among cases and controls

Variables	Frequency		t-test*	P-value
	Cases =42	Controls =42		
FT3 (Pmol/l) Mean ± SD	4.37 ± 0.69	7.81 ± 0.57	24.82	<0.001 HS
FT4 (Pmol/l) Mean ± SD	12.92 ± 1.4	19.62 ± 2.5	14.69	<0.001 HS
TSH (µIu/ml) Mean ± SD	8.05 ± 2.11	5.79 ± 1.07	6.2	<0.001 HS

HS: P-value<0.001 is high significant

Table (3): Correlation between thyroid functions and systolic LV functions of cases.

	FT3		FT4		TSH	
	r	P value	r	P value	r	P value
EF	0.09	<0.001(HS)	0.098	0.005 (S)	-0.07	0.04 (S)
FS	0.18	<0.001(HS)	0.165	0.01 (S)	-0.06	0.01 (S)
Pulmonary pressure	-0.07	<0.001(HS)	-0.262	0.02 (S)	0.09	0.001(S)

FT3: Free Triiodothyronin

FT4: Free Tetra iodothyronine

TSH: Thyroid stimulating hormone

S: Significant

HS: Highly Significant

EF: Ejection Fraction

FS: Fraction Systolic

Table (4): Relation between severity of Heart Failure (HF) and thyroid functions among cases.

	ROSS classification			F test	P value
	II N=15	III N=16	IV N=11		
FT3 Mean ± SD	4.8 ± 0.75	4.3 ± 0.68	3.9 ± 0.59	0.917	0.01 S
FT4					0.04

	ROSS classification			F test	P value
	II N=15	III N=16	IV N=11		
Mean ± SD	12.8± 1.8	13.2 ± 1.4	12.9±1.2	0.156	S
TSH					0.005
Mean ± SD	8.1 ± 1.9	8.8 ±1.99	7.5 ± 2.3	1.46	S

FT3: Free Triiodothyronin
 FT4: Free Tetra iodothyronine
 TSH: Thyroid stimulating hormone
 S: Significant

Table (5): Relation between type, outcome of HF and thyroid functions among Cases.

	Type of HF		t- test	P value
	Acute N=24	Chronic N=18		
FT3				<0.001
Mean ± SD	3.92 ± 0.42	4.83 ± 0.57	6.1	HS
FT4				0.61
Mean ± SD	13.2±1.62	12.8 ± 1.16	0.516	NS
TSH				0.734
Mean ± SD	8.15 ± 2.3	7.9 ± 1.9	0.346	NS
outcome	Outcome of HF		t- test	P value
	Dead N=7	Survived N=35		
FT3				0.01
Mean ± SD	3.8 ± 0.57	4.4 ± 0.699	1.35	S
FT4				0.328
Mean ± SD	12.2±1.82	13.1± 1.3	1.05	NS
TSH				0.117
Mean ± SD	9.4± 2.25	7.8± 2.0	1.76	NS

FT3: Free Triiodothyronin
 FT4: Free Tetra iodothyronine
 TSH: Thyroid stimulating hormone
 HS: P-value<0.001 is high significant
 NS: Non Significant
 S: Significant

Figure (1): Conventional LV systolic functions where EF is Ejection Fraction and FS% is Fraction of Shortening.

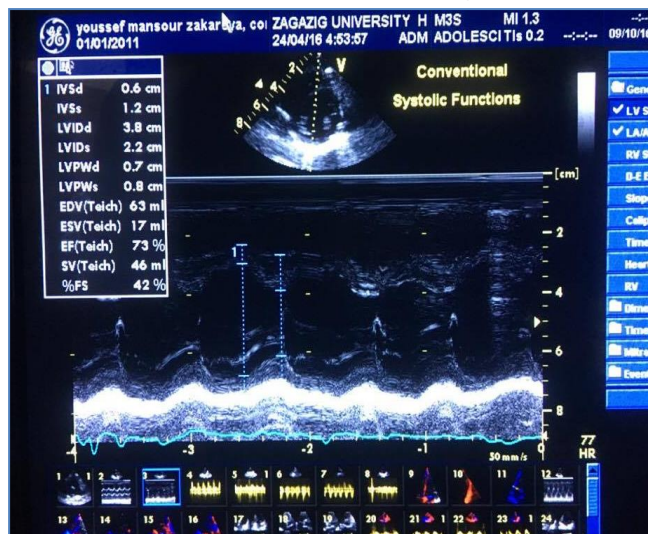
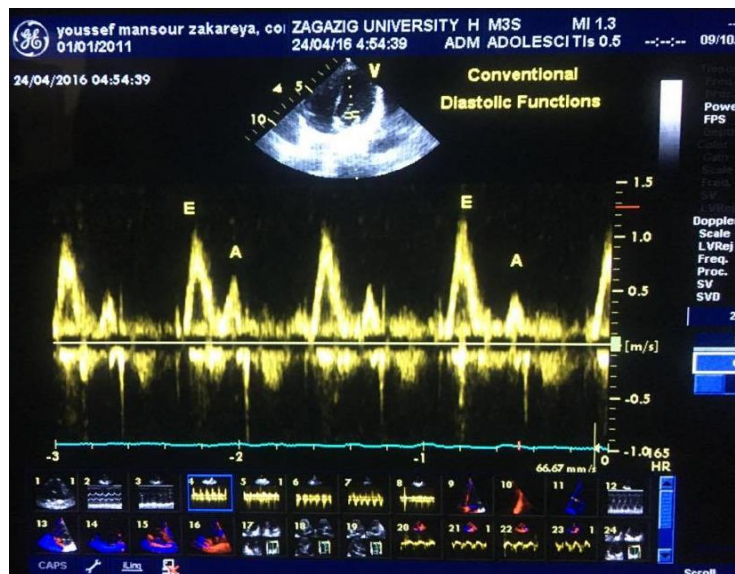


Figure (2): Transmitral inflow velocity of LV, including peak early mitral inflow velocity (E) and peak late mitral inflow velocity (A).



DISCUSSION

Heart failure is considered one of the most serious cardiovascular diseases which have high mortality and morbidity especially among children as they have high hospitalization rate and poor prognosis. Detection of factors that may affect the severity of heart failure and take them in our consideration is the base for good management and improving risk stratification of death from heart failure[19].

Pediatric heart failure (PHF) is now being increasingly recognized as an important source of health care resources utilization with 11,000 to 14,000 heart failure related hospital admission in the United States every year[2]. On assessing diastolic functions by conventional echocardiography, we recorded significant decrease of early atrial mitral inflow velocity (A) and the ratio (E/A) in our HF patients in comparison with their controls.

According to **Dilveer and Michael [20]** which investigated mitral flow velocities, they found that under normal conditions, the E velocity was greater than A velocity, as the ventricle became less compliant as in HF, the E velocity decreased and the ratio became lower. On measuring conventional systolic functions by Echocardiography in our study we revealed that the mean of ejection fraction (EF) of our patients was 52.3% versus 78.95% in controls which showed highly significant difference, our results were in agreement with **Jayaprasad,[21]** who reported that LV dysfunction in children is currently defined by an ejection fraction less than 55%.

In our study (table 1) the mean of fractional shortening (FS%) in cases was 33.2% versus 46.3% in controls which showed also highly significant difference. That result was nearly in agreement with the findings in **Mohammed et al., [22]** which showed that the mean of FS% in HF patients was 33.93% .

In the same context, **Kusumoto and Miyata,[23]** reported significantly decreased both EF% and FS% in pediatric patients with heart failure.

Our study reported that there was a statistically significant difference among both studied cases and control group regarding FT3, FT4 and TSH, as both FT3 and FT4 were significantly lower among studied cases than their controls and TSH was higher among cases.

This was agreeing with **Kiran et al.,[24]** who reported that low FT3 was the commonest abnormality followed by high TSH and low FT4 in critically ill patients admitted in wards and intensive care units (ICUs) at time of admission irrespective of diagnosis with exclusion of previous thyroid disorders and those with family history.

Also, this agreed with **Iervasi et al., [10]** who showed that low serum T3 concentrations, are a common finding found in patients with nonthyroidal illnesses, including cardiac disorders as low T3 circulating levels were found in 30% of 173 consecutive cardiac patients who underwent thyroid function profile evaluation.

Our study showed that there was a statistical significant association between all thyroid

functions (FT3, FT4, TSH) and echo findings including EF, FS, pulmonary pressure. This was in agreement with **Hamilton et al., [25]** study who reported that the degree of FT3 abnormality was clearly related to the ejection fraction and all haemodynamic variables like ejection fraction and mean pulmonary artery pressure that were worse in the patients with low FT3.

Our study showed that there was statistically significant relation between all thyroid functions and Ross classification for severity of heart failure, it was found that mean values of serum FT3 and FT4 in grade IV was significantly lower than those in grade II, III. While mean values of TSH was higher in grade IV as compared to values of grade II, III. So we concluded that the more severe the heart failure, the more the impairment of thyroid functions.

This was partially in agreement with the study of **Iervasi et al., [10]** which classified patients according to NYHA and showed that the prevalence of low FT3 levels was found in patients with NYHA class III-IV illness compared with patients with NYHA class I-II. Our study showed that there was statistically significant relation between type of heart failure and only FT3 as the mean of FT3 was lower in acute cases than chronic cases. This was in agreement with the study of **Grais and Sowers,[26]** which showed that FT3 was lower among acute cases than chronic cases of heart failure, also with **Chen et al., [27]** and **Okayama et al., [28]** which showed that low FT3 level is a target or severity marker of ADHF as Low FT3 levels must induce heart failure, because thyroid hormones affect various organs and cells and are associated with maintenance of normal cardiac function.

Our study showed that there was statistically significant relation between only FT3 and outcome of HF as the mean of FT3 in cases who died was lower than the mean of FT3 in survived cases which was in agreement of the study of **Iervasi et al., [10]** which showed that low T3 syndrome is a strong prognostic predictor of death in patients with heart disease.

This was also in agreement with the study of **Pingitore et al.,[11]** which investigated triiodothyronine levels as a risk stratification for patients with heart failure and showed that those who died had worse cardiac function and lower T3 levels, than those who survived during follow-up. So, T3 measurement offers a number of advantages it is a simple,

inexpensive, and reliable blood test that can be measured at most medical laboratories, unlike several other biohumoral markers like serum norepinephrine levels[29].

According to the importance of thyroid function testing in HF, Mullis-Jansson and his colleagues had used parental T3 as a treatment for HF and showed in their study that parenteral T3 leads to improved postoperative function, reduced the need for inotropic agents and mechanical devices, decreased the incidence of myocardial ischaemia and decreased the incidence of atrial fibrillation and pacemaker therapy [30].

CONCLUSION

According to the results of our study, thyroid function can be altered in pediatric heart failure and this alteration in thyroid function may be related to the severity of heart failure and worse outcome. So, assessment of thyroid function especially FT3 for infants and children with heart failure due to congenital heart disease at hospital admission may be particularly helpful in predicting outcome of heart failure.

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