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A Review of Literature on the Adverse Effects of Hyperthyroidism on the Heart Functional Behavior

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Abstract: Thyroid hormones play an important role on the physiological chemistry of heart and vascular systems in healthy subjects. Any thyroid disorders accompanied with alteration of effective concentration of thyroid hormones cause heart dysfunctions. Thyrotoxicosis is a term given for the clinical manifestation of hyperthyroidism which can invoke heart and vascular abnormalities through the mechanism at heart muscle cells nuclear level. Thyrotoxicosis can play positive roles for heart disorders including atrial fibrillation, left ventricular hypertrophy and right ventricular systolic dysfunction, which are considered as major risk factors for heart abnormalities. Miscalculation of heart dysfunctions related thyrotoxicosis in cardiovascular patients might be avoided through careful laboratory measurements of T4 and T3 to exclude any possible thyroid hormone-related heart diseases.

Key words: Thyroid hormones, thyrotoxicosis, heart dysfunction

INTRODUCTION

Thyroid produce two important hormones of tetraidothyronine or thyroxine (T4) and triido-thyroxine or (T3) but it is the T3 which can be considered as the potent hormone direct the normonal physiology of the heart system. The T4 and T3 both are synthesized within the thyroid gland but T3 itself can be produced from deidonation of T4 in peripheral tissue whether T3 which in stimulating heart is originating from thyroid or it is synthesized from T4 within the heart muscle is not a matter for any critical argument but how thyroid hormones can direct the patho-physiology of heart function which is the prime concern and will be elaborated.

Thyrotoxicosis which is definition for collective clinical manifestation of hyperthyroidism, are among cause of heart morbidity and mortality and thyroid hormones excess are responsible for many cardiovascular diseases (Kaminski *et al*., 2012; Kim *et al*., 2011; Brandt *et al*., 2011; Mansourian, 2010a, b; Everts *et al*., 1996; Brent, 1994; Makino *et al*., 2012; Parma *et al*., 1995; Emrich *et al*., 1993). The eventual outcome of thyroid hormone on heart muscles is through the hormonal action on myocyte predispose mainly to the T3, which is universally is accepted pathway, happen through penetration of T3 through cell membrane and binding to the specific receptors partly believed to be located within the nucleus of target cells. The combined T3-Receptor is behaving similar, to steroid hormones, bind to the specific site on the DNA of heart muscle cells. (Mansourian, 2010a, b, 2012; Kim *et al*., 2011; Mansourian, 2010a, b; Studer and Ramelli, 1982; Studer *et al*., 1989; Bogazzi *et al*., 1999; Klein and Hong, 1986; Klein, 1990; Park *et al*., 1997; Polikar *et al*., 1993).

Therefore, it can be confidently mentioned that T3 stimulate its mechanism at cellular level, with subsequent gene expression of particular proteins within the cardiovascular cells and there are various reports in this area of heart physiology (Klein and Ojamaa, 2000; Morkin, 1993; Dratman and Grodon, 1996; Nayak and Burman, 2006; Maji, 2006; Shimatsu *et al*., 1999).

Following T3 physiological action at myocytes of heart muscle, proteins are translated from transcripted messenger ribonucleic acid (mRNA) and those protein play the vital role in heart functions and various physiological process within cardiovascular systems. In a postulated scenario, when the respected gene within the myocytes is not activated due to the either of T3 under production or even diminished T3 receptor within the myocytes, the adverse effects include many disorders ranging from abnormality in contraction and calcium regulation in cardiac muscle occur due to the alteration of myosin synthesis and enzyme level responsible for calcium (Mansourian, 2012; Mansourian, 2010a, b; Fadel *et al*., 2000; Brent, 1994; Ojamaa *et al*., 1996; Morkin, 1993; Magner *et al*., 1988; Dillmann, 1990; Mintz *et al*., 1991; Kiss *et al*., 1994; Ojamaa *et al*., 2000; Kiss *et al*., 1998; Ladenson *et al*., 1992; Klein and Ojamaa, 2000).

Calcium- ATPase, is a enzyme responsible for active relocation of ionized calcium (Ca^{2+}) into sarcoplasmic reticulum and it is the vital factor for the critical physiological pathways of myocytes, namely known as systolic diastolic function of the heart (Mansourian, 2012; Taillard *et al*., 2011; Little *et al*., 1990; Gillebert *et al*., 2000; Wong *et al*., 2011; Dillmann, 1990; Mintz *et al*., 1991; Kiss *et al*., 1994). The relocation of Ca^{2+} into the sarcoplasmic reticulum of myocytes is occurred through some transport protein which is produce by the metabolic action of T3 on the myocytes. In thyroid related diseases, which can be varied and cab be due to many disorders within thyroid gland itself if it is primary thyroid dysfunction and secondary on cases the other factors causing the alteration of thyroid hormones cardiac diastolic procedures maybe modified with eventual disruption of heart function (Mansourian, 2012; Dillmann, 1990; Mintz *et al*., 1991; Kiss *et al*., 1994; Ojamaa *et al*., 2000; Bogazzi *et al*., 1999; Kinney *et al*., 1988; Karger and Fuherer, 2008; Cooper, 2003; Persani *et al*., 2000).

Phospholamban is the protein responsible for the Ca^{2+} relocation, within cardiac myocytes into sarcoplasmic reticulum which is mediated by calcium-activated ATPase. It seems any function to modify the level of phospholamban eventually lead to the disruption of relaxation which is the proposed physiological role, for diastolic function (Kim *et al*., 2011; Kaminski *et al*., 2012; Kiss *et al*., 1994; Ojamaa *et al*., 2000; Kiss *et al*., 1998; Mintz *et al*., 1991).

Also thyroid hormone play key role in systolic diastolic function through ionized calcium Ca^{2+} release and the subsequent re-uptake by the sarcoplasmic reticulum but other proteins are produced by the action of thyroid hormone at cardiac myocyte within the heart which ultimately are playing key roles in the regulation of the either of electrochemical and mechanical function of heart muscles (Mansourian, 2010c, 2012; Gick *et al*., 1990; Ojamaa *et al*., 1999).

In addition to what was mentioned about the key role of T3 on cardiac myocytes and producing proteins such as myosin to have structural responsibilities and calcium- activated ATPase and related protein for release and re-up taking of ionized calcium into the sarcoplasmic reticulum. T3 also have other function on the heart muscle, independent of gene and nuclear level; including modification of ionized sodium, potassium and calcium channels in the heart muscle to the extend, which, can eventually regulate the well being of heart myocytes in normal physiological conditions. The elevation and suppression in the amount of thyroid hormone and the alteration of above parameters directly will relate to the heart biochemical and physiological pathway changes which eventually lead to cardiac disorders (Mansourian, 2010a, b; Hendriksen and Petersen, 1995; Petretta *et al*., 2001; Diao *et al*., 1998; Roffi *et al*., 2005; Aksnes, 1994; Kaminski *et al*., 2012; Chen *et al*., 2006; Hurley *et al*., 1981; Schmidt-Oft and Ascheim, 2006; Yue *et al*., 2011).

Accordingly, it seems, any alteration in the amount of T3 which can be due to many thyroid dysfunction and even therapeutic regiment leading to thyrotoxicosis can subsequently alter the normal physiological mechanism of heart function. In case of hyperthyroidism, which is the purpose of this review, the structural and regulation of cardiac function modified, to the extend that increased cardiac rate and increased in blood volume, pulse pressure, increased heart out put volume. are among some irregularities of elevated T3 with its subsequent function on the heart muscles (Mansourian, 2010a, b; Waring *et al*., 2012; Kaminski *et al*., 2012; Kim *et al*., 2011; Brandt *et al*., 2011; Davis and Davis, 1993; Walker *et al*., 1994; Klemperer *et al*., 1996; Graettinger *et al*., 1959; Biondi *et al*., 1994; Mintz *et al*., 1991; Klein and Ojamma, 1998; Cacciatori *et al*., 1996; Nordyke *et al*., 1988; Polikar *et al*., 1993; Graettinger *et al*., 1959; Feldman *et al*., 1986; Klein and Ojamaa, 2000).

The eventual consequence of thyroid hormone on the heart function can be based on the physiological elevation rate of left ventricular of systolic- diastolic contraction. As it was mentioned earlier later pathway occurred through the straight metabolic effect of T4 and T3 on heart myocytes cell, with the production of protein responsible for the contraction and other physiological function which is mediated through ionized Calcium regulatory mechanism (Bird-Lake, 2011; Yue *et al*., 2011; Schmidt-Oft and Ascheim, 2006; Wong *et al*., 2011; Diao *et al*., 1998; Little *et al*., 1990; Taillard *et al*., 2011; Aksnes, 1994; Franklyn and Gammage, 2007; Gillebert *et al*., 2000; Morkin, 1993; Ojamaa *et al*., 2000; Kiss *et al*., 1994), THCS, (Dillmann, 1990; Wong *et al*., 2011). There are also some reports concentrating on the role of hyperthyroidism on the atrial fibrillation although the rate of incidence is not large but excess thyroid hormone, on heart can be followed with adverse clinical presentation, among them including atrial fibrillation and ventricular dysfunction (Roffi *et al*., 2005; Fadel *et al*., 2000; Hendricksen and Petersen, 1995; Dahl *et al*., 2008; Brandt *et al*., 2011; Kaminski *et al*., 2012; Dillmann, 1990; Klein 1990; Forfar *et al*., 1982; Klein and Ojamma, 1998).

In general excess T4 and T3 eventually can alter the normal path of heart physiological function therefore it seems many heart diseases can be prevented, if the excess

thyroid hormones of T4 and T3 production and particularly T3 from thyroid gland can be controlled through therapeutic regiments. It seems many undesired heart malfunction possibly can be prevented by treatment of thyroid gland to stop the biosynthesis of extra thyroid hormones (Mansourian, 2010a-c; Fadel *et al*., 2000; Kaminski *et al*., 2012; Roffi *et al*., 2005; Yu and Bilezikian, 2000; Aksnes, 1994), (2,4,8,34, THCS). Klein (1990), Polikar *et al*. (1993), Mintz *et al*. (1991), Klein and Ojamma (1998), Gilligan *et al*. (1996), Feldman *et al*. (1986) and Klein and Ojamma (1998).

Overt hyperthyroidism: Hyperthyroidism clinically is a condition in which thyroid produce elevated amount of thyroid (T4) and triiodothyronine (T3). The metabolic pathways to their production is extensively studied (Mansourian, 2010a, b; Mansourian, 2011a-c; Dratman and Grodon, 1996; Parma *et al*., 1995; Emrich *et al*., 1993).

Thyroid stimulating Hormone(TSH) is a pituitary hormone which after binding to its receptor on thyroid and producing cyclic adenosine monophosphate (cAMP) biochemical process within the thyrocyte membrane is occurred and adenylate cyclase is activated. The latter enzyme is responsible for the production of cAMP from, adenosine triphosphate (ATP). In euthyroid subject there is a correlation between the production of thyroid hormones T4, T3 and TSH, based on the thyroid hormone reference range defined from the laboratory thyroid hormone kit guidelines (Cooper, 2003; Karger and Fuherer, 2008; Dratman and Grodon, 1996; Persani *et al*., 2000; Karger and Fuherer, 2008; Bogazzi *et al*., 1999; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2010a, b; Mansourian *et al*., 2011; Mansourian and Ahmadi, 2010; Mansourian *et al*., 2010a; Mansourian, 2011a, b, 2012; Studer and Ramelli, 1982; Studer *et al*., 1989; Bogazzi *et al*., 1999; Kinney *et al*., 1988). As thyroid gland begin to synthesis elevated amount of T4 and T3. The TSH concentration suppressed due to negative correlation between thyroid hormones of T4, T3 and TSH. It is widely believed that thyroid hormone mainly positively interfere with various metabolic pathways and during healthy state, human thyroid gland produce, a steady thyroid hormone required for normal physiological concentration. In case of elevated concentration of T4 and T3, are occurred due to various factors, it will be associated with signs and syndromes well known as thyrotoxicosis. The clinical manifestation accompanied with thyrotoxicosis are many including heart abnormality, weight loss, anxiety, nervous system disorders, psychological abnormalities, heat resistance, muscle disorders, gastrointestinal abnormality, skin disorders are among the clinical disorders of hyperthyroidism, also the suppression of thyroid hormones which originated from many disorders and other multi-factorial cases and may cause the reverse scenario of hyperthyroidism should also be taken into consideration (Cooper, 2003; Persani *et al*., 2000; Mansourian, 2010a; Nayak and Burman, 2006; Shimatsu *et al*., 1999; Mansourian *et al*., 2008; Mansourian, 2010b, e, f). The physiological and environmental changes among them nutritional malfunction and other physiological cases including pregnancies and metabolic and non metabolic disorders and the therapeutic regiments and possible other interferences must be under surveillance for the proper management of heart -thyroid hormones related diseases (Waring *et al*., 2012; Mansourian *et al*., 2007; Mansourian, 2011c; Rendon, 2005; Tajik and Nazifi, 2011; Franklyn and Gammage, 2007; Mansourian, 2010f; Mansourian *et al*., 2008; Rendon, 2005; Tajik and Nazifi, 2011; McGrowder *et al*., 2006).

The heart disorders originated from thyrotoxicosis include increasing heart beat and output, in which is greatly irrespective of the metabolic rate (Brandt *et al*., 2011; Kim *et al*., 2011; Mansourian, 2012; DeGroot and Leonard, 1970) although, thyrotoxicosis can cause heart abnormality by itself (Levine and Sturgis, 1924; Likoff and Levine, 1943) but also it can further disrupt and badly manipulate, the heart disorder which was already present. (Brandt *et al*., 2011; Sandler and Wilson, 1959; Summer and Surleas, 1961; Ikram, 1985; Magner *et al*., 1988). Thyrotoxicosis play a fundamental modification role on cardiovascular system resulting in the elevation of basic metabolic rate, with undesired blood circulation and increased blood volume to the extent that heart normal physiological pathway is altered (Makino *et al*., 2012; DeGroot and Leonard, 1970; Chaudhury *et al*., 1987; Kim *et al*., 1987).

Heart and hyperthyroidism: It seem there are a close metabolic pathways between the function of excess thyroid hormones and extra adrenaline and noradrenalin and it seem possible, that thyroid hormone and catecholamine elevation have a simultaneous package on heart function and these two system behave on heart physiological process. There are some hints in literature that the thyroid hormones elevation enhance the biological activity of adrenaline and noradrenalin, it is also reported that (Kim *et al*., 2011; Mansourian, 2010a; Roffi *et al*., 2005; Fadel *et al*., 2000; Karger and Fuherer, 2008; Persani *et al*., 2000; Cooper, 2003; Levey and Klein, 1990).

As it was mentioned earlier the main function of T4 and T3 on heart muscle is through the gene expression elevation with subsequent protein production including,

those protein located on the cell surface mainly named receptors including catecholamine receptor on the myocytes. Some reports indicate, the over activity of heart muscle following thyrotoxicosis is due to direct action of thyroid hormone in synthesising elevated amount of adrenaline and noradrenaline receptor on myocytes with the subsequent elevatory action of catecholamines, on the heart muscle (Mansourian, 2011a; Makino *et al*., 2012; Mansourian, 2010f; Levey and Klein, 1990; Mansourian, 2010e).

The combined effect of thyroid hormones and catecholamine on the heart function, resulted into the elevation of blood volume, which take place by over -load of heart function much higher than its normal physiological capacity with subsequent heart failure which can be reversed following thyroid returning to normal function following medical treatments (Franklyn and Gammage, 2007; Kannel *et al*., 1998; Kim *et al*., 1987; Forfar *et al*., 1982). Thyroid hormones excess and eventual heart failures which is accompanied with thyrotoxicosis not only lead to heart hypertrophy which is eventually directed to increasing systolic contractibility and diastolic relaxation but also ends up with, atrial fibrillation (Levy, 2002; Forfar *et al*., 1979; Monreal *et al*., 1988; Staffurth *et al*., 1977; Sandler and Wilson, 1959; Summers and Surtees, 1961; Ikram, 1985; Magner *et al*., 1988; Levine and Sturgis, 1924; Likoff and Levine, 1943).

The mechanism behind biochemical effect of T4 and T3 on atrial fibrillation also is not fully understood but hyperthyroidism interfere with proper function of atrial pathway within the heart muscle (Sandler and Wilson, 1959; Summers and Surtees, 1961; Ikram, 1985; Levine and Sturgis, 1924; Likoff and Levine, 1943; DeGroot and Leonard, 1970; Freedberg *et al*., 1970).

How thyrotoxicosis affect the heart: It seems palpitation is among the signs which in some occasion is clinically manifest itself with thyrotoxicosis. Although, there are an interrelation ship metabolic pathways between central nervous system and thyroid in respect to heart myocytes behavior but it is widely believed that, heart beat can be elevated among thyrotoxic patients even when they receive B-blocker to inhibit the function of catecholamines (Cacciatori *et al*., 1996).

Although, there are not a clear- cut rate of incidence of heat atrial fibrillation among subjects with thyrotoxicosis but it is widely believed that about 5-22% of patients with thyrotoxicosis may have the clinical manifestation of atrial fibrillation but the same heart disorder among non- thyrotoxic patients is reported to be less than even 1% (Sandler and Wilson, 1959; Summers and Surtees, 1961; Ikram, 1985; Levine and Sturgis, 1924; Likoff and Levine, 1943; DeGroot and Leonard, 1970; Freedberg *et al*., 1970; Iwasaki *et al*., 1989; Petersen and Hansen, 1988; Ostrander *et al*., 1965; Nordyke *et al*., 1988).

It seems T3 related thyrotoxicosis is much more potent in causing heart disorder (Ostrander *et al*., 1965).

The prevalence of atrial fibrillation is higher among quarter of older in general population of male and female of more than sixty years of age (Hak *et al*., 2000; Mitrou *et al*., 2011; Mansourian *et al*., 2010a).

Although, heart disorders and among them artial fibrillation presentation can be considered as a common clinical manifestation of thyrotoxicosis but this area of investigation is not clearly cut and defined elaboration about the role of excess thyroid hormone on atrial fibrillations are not properly understood and the findings, in this area of research are shaky and even with laboratory measurements of thyroid related hormone of TSH, T4 and T3 and subsequent comparison of these latter hormones with the manifestation of atrial fibrillation, one can get not proper understanding and is not able to comment clearly on a precise overtook in this area of thyroid-heart patho-physiology (Kannel *et al*., 1998; Levy, 2002; Hendriksen and Petersen, 1995; Hurley *et al*., 1981; Giladi *et al*., 1991; Tajiri *et al*., 1986; Forfar *et al*., 1979; Forfar *et al*., 1979; Staffurth *et al*., 1977).

Thyrotoxicosis manipulate heart ventricular: Hyperthyroidism is associated with cardiovascular disorders which in some cases leading to mortalities. It is reported that the Left Ventricular Hypertrophy (LVH) may be the major risk factor for the mortality in subjects affiliated with thyrotoxicosis. There are various reports indicating thyrotoxicosis adversely affect heart function and it may eventually cause the disorder on the LVH. There are documented reports on the role of thyroid hormone on the physio- pathological behavior of heart function and as it was already mentioned thyrotoxicosis may eventually disrupt the normal physiological pathway of cardiovascular system including the elevation of myocyte contraction (Henderson *et al*., 2009; Diao *et al*., 1998; Little *et al*., 1990; Taillard *et al*., 2011; Yue *et al*., 2011; Bird-Lake, 2011).

The reduction of myocyte and vascular resistance, an increase in the level of heart output, the disruption of heart beat arrhythmias including sinus tachycardia atrial and ventricular disorders and eventually atrial fibrillation can be among the abnormality with hyperthyroidism and its eventual clinical manifestation well known as thyrotoxicosis (Chen *et al*., 2006; Kaminski *et al*., 2012).

It seems that thyroid hormone function tests which are carried out by medical diagnostic laboratory are the

key factors in labeling the hyper thyroid patients, hyperthyroidism defined when TSH is suppressed lower than reference range of laboratory manual kit but with elevated thyroid hormones of either T4, T3 or both hormones (Mansourian, 2010a, b; Emerson and Utiger, 1972; Emrich *et al*., 1993; Studer and Ramelli, 1982; Karger and Fuherer, 2008; Cooper, 2003; Persani *et al*., 2000; Nayak and Burman, 2006; Maji, 2006; Makino *et al*., 2012; Shahmohammdi *et al*., 2008; Mansourian and Ahmadi, 2010). The overt hyperthyroidism which is associated with suppressed TSH and elevated T4 and T3 may clinically accompanied with clinical manifestation collectively known as thyrotoxicosis. The elevated T4, T3 and particularly T3 in case of heart can have an adverse side effects on the heart muscle and vascular system. Thyrotoxicosis may eventually end up with fatal scenario. Left ventricular hypertrophy is one of serious fatal conditions among the adverse effects of excess thyroid hormone in this area of cardiovascular pathophysiology are thoroughly investigated (Kim *et al*., 2011; Mansourian, 2012; Kannel and Cobb, 1992; Haider *et al*., 1998; Shirani *et al*., 1993; Kobori *et al*., 1999; Petretta *et al*., 2001; Degens *et al*., 2003; Hu *et al*., 2003; Donatelli *et al*., 2003).

It is believed LVH itself independently of other cause of cardiovascular disorders have a fatal outcome for the heart muscle and vascular diseases including atherosclerosis, heart failure, ventricular irregularities and unpredicted death due to cardiovascular disorders (Little *et al*., 1990; Bird-Lake, 2011; Diao *et al*., 1998; Taillard *et al*., 2011; Roffi *et al*., 2005; Schmidt-Oft and Ascheim, 2006; Makino *et al*., 2012; Mansourian, 2010d; Mansourian *et al*., 2008; Kannel and Cobb, 1992; Haider *et al*., 1998).

Also it seems that thyrotoxicosis proved to be mainly responsible for many from of cardiovascular disease including left ventricular hypertrophy and eventual fatal outcome also there are some argument and controversial discussions about the definition of hyperthyroidism from laboratory point of view. These latter studies indicated and concentrate on the laboratory findings of TSH and argued that at some period the suppressed TSH level and cardiovascular disorder particularly LVH may not have direct correlation (Mansourian *et al*., 2007; Parle *et al*., 2001; Tunbridge *et al*., 1977; Hollowell *et al*., 2002). In my opinion the thyroid function can only be assessed only after careful examination of TSH, T4, T3 and following determination of all of three hormones and examination of thyroid hormone receptor only at that time one can label for sure, the hyperthyroid patient precisely. Therefore arguments about the nutritional status of one society including the iodine status do not help in the argument about the adverse effect of thyrotoxicosis on the cardiovascular system (Mansourian, 2011a; Mansourian *et al*., 2007; Mansourian, 2011b; Makino *et al*., 2012; Tunbridge *et al*., 1977; Hollowell *et al*., 2002). One other careful consideration in this area of research is the therapeutic drug regiment which can possibly interfere with available data and poised itself for possible misdiagnosis in the management of thyrotoxic heart diseases (Franklyn and Gammage, 2007; Wong *et al*., 2011; Mansourian, 2012; Mansourian, 2010a, f).

Studies indicated it seems that LVH incidence among general population to be about 10% but the same index for LVH for thyrotoxic patients is more than 5 times of general population (Little *et al*., 1990; Taillard *et al*., 2011; Roffi *et al*., 2005; Schmidt-Oft and Ascheim, 2006; Hak *et al*., 2000). Various other studies are in agreement with the adverse effects of thyrotoxicosis on the cardiovascular functions including LVH (Biondi *et al*., 1996; Biondi *et al*., 1993; Dillmann, 1990; Kinugawa *et al*., 2001).

Also the roll of excess thyroid hormone on the malfunction of cardiovascular, system is well documented, other related factors including older age, obesity and increased body mass index and pulse pressure abnormalities in absence excess thyroid hormone can also separately play the key roles on the initiation of LVH with T4 and T3 intervention (Waring *et al*., 2012; Kaminski *et al*., 2012; Kannel and Cobb, 1992; Coca *et al*., 1999; Schirmer *et al*., 1999). In according to earlier findings, it seems that women are more prone to LVH, due to higher incidence of hyperthyroidism among female population and other possible factors in this regards, also this argument is not universally agreed on (Mansourian, 2012; Mansourian *et al*., 2008, 2010a; Mansourian, 2010a, b, e, f; Coca *et al*., 1999; Schirmer *et al*., 1999).

Although, LVH seems to be the main complication in thyrotoxicosis but there are reports indicating the Right Ventricular Systolic Dysfunction (RVSD) also can be considered one of the adverse effect of hyperthyroidism.

There are documented report which demonstrate the cardiovascular lesion associated with thyrotoxicosis mainly related to LVH but as it was mentioned earlier, it seems there are heart malfunction, which effect both LVH and RVSD (Weissel, 2001; Raddino *et al*., 2001; Di Giovambattista, 2008; Dahl *et al*., 2008; Klein and Ojamma, 2001; Umana *et al*., 2003; Siu *et al*., 2007; Di Giovambattista, 2008).

There are other studies indicating that RVSD can be considered as an independent and isolated cardiac disorder and it is not certain whether should the LVH and

RVSD malfunction happen on the same time when thyrotoxicosis adversely effect cardiovascular system (Dahl *et al*., 2008; Simko *et al*., 2004; Kaminski *et al*., 2012; Chen *et al*., 2006; Kaminski *et al*., 2012; Nadkarni *et al*., 2008; Lozano and Sharma, 2004; Cohen and Schattner, 2003; Park *et al*., 2006; Lozano and Sharma, 2004; Nakchbandi *et al*., 1999; Syriou *et al*., 2008).

As it was mentioned the right ventricular RVD, does play a major risk factor for the heart failure, right and left ventricular dysfunction not necessarily happen parallel to each other (Dahl *et al*., 2008; Cohen and Schattner, 2003; Park *et al*., 2006; Lozano and Sharma, 2004; Nakchbandi *et al*., 1999; Syriou *et al*., 2008; Kang *et al*., 2009).

Although, it seems the thyrotoxic side effect of thyroid hormone on the muscle cells are adequately established in causing the elevation of heart rate, left ventricular dysfunction lowering vascular resistance enhancing Sodium re-absorption and elevating the production of hormone responsible for blood cell formation but the metabolic pathway to the RVD in cardiovascular system during hyperthyroidism, does play a different path compared to the former signs and systems within the cardiovascular system (Schmidt-Oft and Ascheim, 2006; Bird-Lake, 2011; Raddino *et al*., 2001; Di Giovambattista, 2008; Nadkarni *et al*., 2008; Dahl *et al*., 2008; Klein and Ojamma, 2001; Pereira *et al*., 2000; Kwak *et al*., 2004; Kiss *et al*., 1994).

How atrial fibrillation can be initiated by thyrotoxicotic: Atrial Fibrillation (AF) is a thyrotoxicotic related malfunction, take place through ionized calcium irregularity within myocytes with eventual heart dysfunction (Hurley *et al*., 1981; Kannel *et al*., 1998; Bielecka-Dabrowa *et al*., 2009; Dahl *et al*., 2008; Klein and Ojamma, 2001; Umana *et al*., 2003). On condition that thyrotoxicosis persist for enough period of time can effectively cause atrial fibrillation which can be associated with LVD. The combination of atrial fibrillation, Sinus tachycardia and left ventricular dysfunction, consequently lead to tachycardia with eventual disorders in the heart physiology causing the pathological disturbance of heart muscle (Levy, 2002; Monreal *et al*., 1988; Raddino *et al*., 2001; Di Giovambattista, 2008; Umana *et al*., 2003; Siu *et al*., 2007). As Atrial fibrillation is a condition with eventual fatal scenario due to heart beat disturbance which may induce blood coagulation with the cardiac itself with subsequent fatal picture of cardiovascular system (Diao *et al*., 1998; Forfar *et al*., 1979; Staffurth *et al*., 1977; Banach *et al*., 2007a; Mariscalco *et al*., 2008; Staffurth *et al*., 1977). It seems excess thyroid hormone in some subjects which are prone to hyperthyroidism lead to atrial fibrillation and the incidence of atrial fibrillation among thyrotoxic patients, are greater than non-thyrotoxic subjects within the normal society and it seems is more common among male hyperthyroid patients, particularly T3 type of thyrotoxicosis. Atrial fibrillation is a heart malfunction directly related to chronological age, various cardiac, vascular and some other disorders Excess thyroid hormone reduce the action potential which can be considered as pre-existing risk factor for the clinical manifestation of atrial fibrillation (Kaminski *et al*., 2012; Yue *et al*., 2011; Kannel *et al*., 1998; Banach *et al*., 2007b; Mariscalco *et al*., 2008; Staffurth *et al*., 1977). Atrial fibrillation is disorder may clinically presented with thyrotoxicosis and usually can be followed by fatal outcome, mainly due to embolism (Hurley *et al*., 1981; Hendriksen and Petersen, 1995; Bielecka-Dabrowa *et al*., 2009; Staffurth *et al*., 1977) and atrial fibrillation may also occur among non- thyroidal disease and normal subjects but thyrotoxicosis aggravate the onset of atrial fibrillation. As it was mentioned earlier, atrial fibrillation is not usually symptom of younger age but patient of more than sixty years of age are more afflicted to atrial fibrillation The age related arrhythmia associated with atrial fibrillation might be lowered among thyrotoxic patient, compared to general population (Mitrou *et al*., 2011; Hak *et al*., 2000; Levy, 2002; Kaminski *et al*., 2012; Chen *et al*., 2006; Weissel, 2001; Agner *et al*., 1984; Mohacsi *et al*., 1990). In a separate study it was found that hyperthyroidism alone based on thyroid hormone measurement can not be a key factor for atrial fibrillation. Cardiovascular disorders and the excess thyroid hormones of T4 and particularly T3 should be carried out for enough period of time to be able to manifest the whole picture of thyrotoxicosis and only on that time atrial fibrillation can be clinically established and manifest itself (Roffi *et al*., 2005; Wong *et al*., 2011; Fadel *et al*., 2000; Staffurth *et al*., 1977; Krahn *et al*., 1996). There are various reports showing in majority of cases with atrial fibrillation, the abnormality can be corrected following thyrotoxic treatment, also this reversion to healthy state is mostly depended to the duration of atrial fibrillation onset and the thyrotoxic severity and patient age (Yue *et al*., 2011; Dahl *et al*., 2008; Northcote *et al*., 1986; Banach *et al*., 2008; Shimizu *et al*., 2002), therefore those subjects with atrial fibrillation of older than sixty years of age should be evaluated for thyroid hormone test through the careful laboratory measurement of suspected person serum to eliminate the possibility of hyperthyroidism for cardiovascular diseases (Mansourian *et al*., 2010a; Mansourian, 2010b, d, e; Shahmohammdi *et al*., 2008; Northcote *et al*., 1986; Banach *et al*., 2008; Shimizu *et al*., 2002; Nakazawa *et al*.,

1982). The laboratory examination of thyroid function test should include TSH, T4, T3 and the measurement of TSH alone without the assessment of T4 and T3 can be misleading in the assessment of thyrotoxic patients and as result of this mistake the cardiovascular diseases related to thyroid abnormality is occasionally miss-interpreted and undetected cardiovascular related thyrotoxic patients might loose the proper pathway to clinical care to recover from heart dysfunctions (Mansourian, 2010a, 2012; Staffurth *et al*., 1977; Nakazawa *et al*., 1982; Forfar *et al*., 1981; Banach *et al*., 2007a; Aras *et al*., 2005).

CONCLUSION

- Thyroid hormones and particularly T3 stimulate the heart myocyte at nuclear level, with subsequent gene expression of particular proteins within the heart cells and producing the proteins which are required for the heart function
- There are various reports in this area of heart physiology indicating any disruption in the amount of thyroid hormones seriously modify heart function adversely, due to disruption in the amount of required proteins responsible for the proper function of heart physiology
- Thyroid hormone and particularly T3 stimulate the production of Calcium- ATPase, which is an enzyme responsible for active relocation of ionized calcium (Ca^{2+}) into myocytes sarcoplasmic reticulum and it is the vital factor for the critical physiological pathways of myocytes, namely known as systolic diastolic function of the heart
- Hyperthyroidism is associated with cardiovascular disorders which in some cases leading to mortalities. Thyrotoxicosis is a term given for the clinical manifestation of hyperthyroidism which can invoke heart and vascular dysfunction through the mechanism at myocyte nuclear level
- Thyrotoxicosis can be considered as risk factor for heart disorders including Atrial Fibrillation (AF), Left Ventricular Hypertrophy (LVH), Right Ventricular Systolic Dysfunction (RVSD)
- It is also reported that the Left Ventricular Hypertrophy (LVH) may be considered the major risk factor for the mortality in subjects affiliated with thyrotoxicosis
- Atrial fibrillation abnormality, can be considered as clinical manifestation of thyrotoxicosis. Atrial fibrillation is considered as a risk factor for embolism and the incidence of cardiovascular disorders commonly higher among thyrotoxic patients
- To Avoid any miscalculation of heart dysfunctions the thyrotoxicosis in cardiovascular patients should be checked through careful measurements T4 and T3 to exclude any thyroid hormone-related heart diseases, by doing that any miss-interpretation and miss-diagnosis of undetected thyrotoxic patients with heart dysfunctions are prevented
- As heart failure is age dependent the thyroid function tests should be carried out for all subjects over sixty of years to exclude heart dysfunction due to possible hyperthyroidism

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