ABSTRACT

Thyroid hormone has a major action on heart and it influences the role on cardiac activity. T3 has powerful contractility property on the heart through the myosin isoforms and calcium proteins. The cardiovascular signs and symptoms of thyroid disease accompany both hyperthyroidism and hypothyroidism. Thyroid hormone action has profound consequences for the heart rate, ranging from atria fibrillation to hemodynamic collapse. However, numerous reports of various electrocardiographic changes indicative of such a risk have been published. There is still an argument going on that whether there is a link between thyroid hormone and cardiovascular diseases. T3 is also used for the heart replacement therapy and has shown the improvement in ventricular performance. In this short review, we have discussed about the thyroid hormone and its effect on heart.

KEYWORDS: Thyroid hormone, Rythmicity, Contractility

INTRODUCTION

The thyroid hormones, triiodothyronine (T3) and thyroxine (T4) are hormones which are tyrosine produced by the thyroid gland are responsible for regulation of basic metabolism of the
cell. T3 and T4 hormones require iodine to a greater extent. One of the largest glands in our body is the thyroid gland which is found in the neck, below the thyroid cartilage. This gland controls how quickly the body uses energy, makes proteins and controls how sensitive the body is to some other hormones. One of the largest glands in our body is the thyroid gland which is found in the neck, below the thyroid cartilage. This gland controls how quickly the body uses energy, makes proteins and controls how sensitive the body is to some other hormones. A deficiency of iodine leads to decreased production of T3 and T4 enlarges the thyroid tissue and will cause the disease known as goiter. The major form thyroid hormone in the blood is thyroxine (T4), which has a longer half-life than T3. The ratio of T4 to T3 released into the blood, is roughly 20 to 1\textsuperscript{[10]}. T3 is in inactive form and T4 is in active form. Hence T4 is present in the peripheral blood. Thyroid gland produces calcitonin, which plays an important role in calcium homeostasis. This gland covers the windpipe from all the three sides. Thyroid hormones T3 and T4 help the body to produce and regulate adrenaline, epinephrine and dopamine. These hormones also have role in neuronal activity of the brain. In the absence of functional thyroid gland, the body would not be able to process carbohydrates and vitamins. This in turn can ultimately lead to weight gain.\textsuperscript{[17]}

The number of heart beats per unit time is known as heart rate. It is expressed as beats per minute. Heart rate can vary according to the body’s physical needs such as the need to absorb oxygen and excrete carbon dioxide. Some of the activities that can provoke change are physical exercise, sleep, illness, ingesting and drugs. Normal heart rate of human ranges about 60-100bpm. If the heart rate is slow that is below 60bpm, it is known as bradycardia. Increased heart rate (100bpm) is referred as tachycardia. If the heart is not beating in a regular pattern, then it is defined as arrhythmia. Sometime abnormalities of heart rate may indicate disease.\textsuperscript{[5]}

Resting sinus tachycardia is the commonest cardiovascular sign of human hyperthyroidism. The increase in heart rate does not remain same during 24hours incidence. But circadian variation is preserved which is more pronounced than in normal subject and which has been reported consistently in patients with overt hyperthyroidism is atrial fibrillation. The important mechanism for the regulation of cardiac output is heart rate. A very high heart rate also increases the rate of myocardial relaxation and myocardial contractility.\textsuperscript{[22]} Increase or decrease in action of thyroid hormone on molecular pathways in the heart causes cardiovascular derangements. Overt hyperthyroidism induces a hyper dynamic cardiovascular state which in turn causes a faster heart rate, left ventricular systolic and diastolic function and increased prevalence of supraventricular tachyarrhythmia such as atrial fibrillation. Subclinical hyperthyroidism results with increased heart rate, atrial arrhythmias, impaired ventricular relaxation and increased risk of cardiovascular mortality.\textsuperscript{[37]}

When the thyroid hormone is in excess amount, it causes palpitations and exercise intolerance to some extent which is due to increased heart rate and fatigue. The changes in heart rate are due to the changes in the nervous system’s control on the heart. The amount of blood pumped by the heart is also increased in hyperthyroidism. This can be seen in patients with weak hearts because this increased workload on the heart muscle may result in heart failure.\textsuperscript{[34]}
ACTION OF THYROID HORMONE IN THE HEART

Interaction with specific nuclear receptors in cardiac myocytes causes the thyroid hormones to act on the heart. Thyroid hormone influences on ion transport functions have been studied in isolated cardiac myocytes and may be independent of protein synthesis. Thyroid hormone function is found to be first binding to nuclear receptors. Such proposed extra nuclear effects are less well characterized than are the interactions of THs with nuclear receptors. Overall, changes in thyroid hormone effect on cardiac action by three different ways (a) the biologically relevant TH, T\(_3\), exerts a direct effect on cardiac myocytes by binding to nuclear T\(_3\) receptors influencing cardiac gene expression; (b) T\(_3\) has sensitivity towards sympathetic system; and (c) T\(_3\) leads to hemodynamic alterations in the periphery that result in increased cardiac filling and modification of cardiac contraction \([25]\). In contrast to humans, rodents do not express the type 2 iodothyronine deiodinase in their myocardium, and conversion of T\(_4\) to T\(_3\) does not occur to any measurable degree in rodent cardiac myocytes \([46]\).

\(\beta\) -ADRENERGIC SYNERGISM

Increased \(\beta\)-adrenergic tone can cause variation in the thyroid activity of some tissues. In the brown adipose tissue of small mammals, adaptive thermo genesis depends both on cold-induced adrenergic stimulation of uncouplingprotein-1, which in turn promotes heat generation by uncoupling oxidative phosphorylation from ATP synthesis, and on adrenergic stimulation of the type 2 iodothyronine deiodinase (D2), which promotes tissue-specific thyrotoxicosis via conversion of thyroxine to 3,5,3\-' triiodothyronine \([49]\). In this case, the cAMP-responsiveness of D2 provides a mechanism by which catecholamine excess can directly cause tissue-specific thyroid hormone excess, a pre-requisite for optimal heat generation \([4]\). Because D2 is also expressed in the human heart \([11]\), \(\beta\)-adrenergic-mediated increases in thyroid status may also occur in this tissue.

One of the major \(\beta\)-adrenergic receptors (\(\beta\)- A R) expressed in the heart are \(\beta\)-AR1 and \(\beta\)-AR2 \([36]\), both coupling to Gs, adenyllyl-cycles-coupled heterotrimeric stimulatory G-protein, which in turn activates the classical cAMP/protein kinases A (PKA) pathway \([55]\). However, while the \(\beta\)-1-AR activates only the d adenylate cyclase activity \([5,40,44]\). One study of baboons treated with thyroid hormone also found increased \(\beta\)-AR number \([20]\). In another study the authors found a temporary increase in \(\beta\)-AR binding capacity in rat ventricle membranes isolated from thyrotoxic rats. The binding returned to normal levels after one month of T4 treatment \([17]\). Only few studies have found there is no change in \(\beta\)-AR in response to thyroid hormone treatment \([18]\). The potential for differential regulation of \(\beta\)-AR1 and \(\beta\)-AR2 by thyrotoxicosis has been studied using cultured ventricular myocytes, with thyroid hormone treatment preferentially increasing the expression of \(\beta\)-AR1 \([57]\). The same group subsequently demonstrated that \(\beta\)-AR1 may be regulated by T3 at the transcriptional level \([3]\), one of the few instances where formal thyroid-hormone responsiveness of an adrenergic signaling gene has been documented. While these and other classical studies are often cited as support for intrinsic adrenergic hyper responsiveness of the myocardium in
hyperthyroidism, due to increases in β-AR number, more recent results from transgenic mice with over expression of beta adrenergic receptors showed that despite the 2 to 400-fold over expression of the receptor, there was no proportional increase in the binding sites or in the receptor stimulated cAMP production \cite{56,18}, suggesting that alterations in other components downstream in the cascade may be necessary for the increased adrenergic responsiveness during thyrotoxicosis.

**EFFECT OF THYROID HORMONE ON HEART RATE**

An important mechanism for the regulation of cardiac output is the heart rate. Apart from determining the rate of cardiac ejection, it affects both systolic and diastolic pressure. An accelerated heart rate increases the minute stroke work at any given level of cardiac preload—a finding consistent with improved myocardial contractility (force-frequency relation). An increased heart rate also increases the rate of myocardial relaxation, thus improving early cardiac filling \cite{6}. However, acceleration of the frequency of cardiac contraction does not increase cardiac performance if preload is not augmented or, at least, maintained constant. Pacing induced increase in contraction frequency generally reduces preload and stroke volume, so that cardiac output remains constant \cite{11,47}. On the other hand, an increased heart rate reduces diastolic filling time and, thus, leads to greater dependence on atrial systole. This explains the important path physiologic impact of atrial fibrillation on cardiac performance. Interestingly, heart rate may also affect peripheral hemodynamic. Studies of arterially paced normal subjects have demonstrated that an increase in the frequency of cardiac contraction reduces the “dynamic” compliance of the arterial tree and augments arterial pressure \cite{45,28}. This effect probably results from altered timing of the reflected pressure wave from the peripheral arterial tree consequent to the reduction in absolute duration of systole. Those is, as systolic time lessens because of increased heart rate, the reflected pressure wave returning from the peripheral arterial tree would be added to and so enhance the forward pressure wave, thereby increasing blood pressure. Thyroid hormone has a positive chronoscopic effect, and resting sinus tachycardia is the most common cardiovascular sign of human hyperthyroidism \cite{39}. The increase in heart rate does not remain constant during 24hour rather; circadian variation is preserved and is even more pronounced than in normal subjects \cite{30}. An increased incidence of atrial fibrillation has also been consistently reported in patients with overt hyperthyroidism. The increase in chronotropism and bathmotropism in hyperthyroid patients is probably caused by unbalanced sympathovagal tone due to a relative rather than an absolute adrenergic overdrive \cite{7}. This interpretation is strengthened by the observation that both catecholamine metabolism and adrenergic cardiovascular responsiveness do not differ substantially from normal in patients with hyperthyroidism \cite{30,31,32,33-41}. On the other hand, the close relation between thyroid hormone level and night heart rate in hyperthyroid patients which is least influenced by sympathetic tone, suggests that thyroid hormone may directly affect SA node excitability \cite{53,54,51}.
THYROID HORMONE AND MYOCARDIAL CONTRACTILITY

Myocardial contractility refers to the intrinsic property of the cardiac muscle to do work that is “the potential to do work” [41]. Thus, it corresponds to the performance of the heart independent of the effect of heart rate and/or loading status sense structre. By contrast, the term “LV systolic function” represents the aggregate effect of all the mechanisms that control cardiac performance (heart rate, preload, after load, and myocardial contractility). In hyperthyroid patients there is a consistent improvement in LV systolic function at rest [9–29, 35,23, 12, 38,42,6–13,14,15, 19,48–50]. There are two schools of thought as to how this finding should be interpreted in terms of myocardial contractility. Controversy is fueled by the different importance given to changes in heart rate and cardiac loading conditions. In studies in which preload and/or after load were considered to be substantially unaffected by thyroid hormone excess, the enhancement of LV systolic function, independent of the effect of heart rate, was viewed as the result of a mandatory increase in the level of myocardial contractility [58, 59,1]. By contrast, in studies in which thyroid hormone was thought to have a pronounced effect on heart rate and peripheral circulation, the presence of an effective increase in myocardial contractility was considered too simplistic. The studies by Merillon et al. [19] and by Feldman et al. are emblematic of the two contradictory interpretations. Merillon et al. [19] assessed LV function in seven thyrotoxic patients by cardiac catheterization in comparison with 11 normal controls arterially paced at a near identical heart rate. They found no differences between the two groups in such parameters of contractile performance as LV ejection fraction, rate of rise of LV pressure as a proportion of the total pressure, velocity of circumferential fiber shortening, and ratio of LV end-systolic pressure to end systolic volume. Conversely, it was noted that atrial pacing, but not hyperthyroidism, was accompanied by a marked reduction in both end-diastolic volume and pressure and by a significant increase in systemic vascular resistance and mean aortic pressure. As expected, cardiac performance was not increased in arterially paced subjects. Although from a path physiological perspective atrial pacing and hyperthyroidism are not strictly comparable (acute vs. chronic condition), the authors concluded that there was no realistic increase in the true level of myocardial contractility independent of changes in heart rate and preload in human hyperthyroidism. This suggested that the high output state was probably due to the synergistic interaction between the increase in heart rate and ventricular preload. In contrast, Feldman et al. [21] studied LV function in 11 hyperthyroid patients by means of echocardiography and in 11 age matched normal subjects. They found no differences between the two groups in LV end-diastolic diameter or in end-systolic meridional wall stress. Differently, the rate corrected mean velocity of circumferential fiber shortening (a measure of LV function claimed to be independent of preload and heart rate) was much higher in hyperthyroid patients.

LOW TRIIODOTHYRONINE SYNDROME AND ITS REPLACEMENT THERAPY IN ACUTE HEART FAILURE.

Patients with dilated cardiomyopathy have been known to be suffering from low T3 syndrome and that its occurrence is absolutely independent[1,16,21,26–43]. Less T3 concentrations on
myocytes gene expression and heart contractility has been seen in a model of low T₃ syndrome in which T₃ supplementation made both the cardiac function and phenotype normal[24]. Low circulating T₃ is due to the reduced activity of 5’–monodeiodinase, which in turn is responsible for converting T₄ into T₃ in peripheral tissues[52].

CONCLUSION:

Thyroid hormone has a lot of beneficial effects on the cardiovascular system. Therefore, the thyroid hormone level should be maintained in a constant manner for proper functioning of the heart.

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