Journal of the Hong Kong College of Cardiology

Volume 13
Issue 1 *October*

Article 5

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Recommended Citation
Chung-Wah Siu, Hung-Fat Tse, Chu-Pak Lau, Thyrotoxic Heart Disease *Journal of the Hong Kong College of Cardiology* 2005;13(1) https://doi.org/10.55503/2790-6744.1118

Thyrotoxic Heart Disease

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SIU ET AL.: ***Thyrotoxic Heart Disease.*** *The close link between the thyroid gland and the heart has been well recognized since the first description of thyrotoxicosis in nearly 200 years ago. Despite this well known association, there have been only a few population based studies performed on thyrotoxic heart disease except thyrotoxic atrial fibrillation. Even so, there has not been any consensus for the definition for "thyrotoxic heart disease". For other cardiac manifestations of thyrotoxicosis including thyrotoxic cardiomyopathy and thyrotoxic pulmonary hypertension, only occasion case reports can be found in the current medical literatures. Their natural history, clinical course and outcomes are largely unknown. On the other hands, there is an enlarging body of evidence suggesting a direct pathogenic role of thyrotoxicosis per se as the sole cause of these thyrotoxic heart diseases. In this review, we briefly discuss the three cardiac consequences of thyrotoxicosis, namely atrial fibrillation, congestive cardiac failure and pulmonary hypertension. (J HK Coll Cardiol 2005;13:16-20)*

Atrial fibrillation, cardiac failure, thyrotoxicosis

摘要

自從近２００年前第一次描述甲狀腺功能亢進以來，甲狀腺疾病和心臟疾病之間的密切關係已經得到了充分的認識。儘管這一關係已經熟知，但是除了甲狀腺功能亢進的房顫外，只有很少人研究甲狀腺功能亢進的心臟疾病。甚至直到今日對於“甲狀腺功能亢進的心臟疾病”還未有統一的定義。關於其他的甲狀腺功能亢進心臟病的表現，包括甲狀腺功能亢進的心肌病和甲狀腺功能亢進的肺動脈高壓，在當今的醫學文獻中只有偶爾個別的病例報道。它們的自然病程，臨床進展和結果在很大程度上還不得而知。另一方面，越來越多的證據表明甲狀腺功能亢進本身，就是引起這類心臟病的唯一而直接的致病因素。在這篇綜述中，我們簡要地討論三種甲狀腺功能亢進的心臟疾病，也就是房顫、充血性心力衰竭和肺動脈高壓。

關鍵詞：房顫　心力衰竭　甲狀腺功能亢進

Introduction

Thyrotoxicosis is a common medical condition with prevalence of 2 percents in female and 0.2-0.3 percent in male.[1] The close link between the thyroid gland and the heart was evident since the first description of thyrotoxicosis for nearly two hundred years ago.[2] Many of the clinical manifestations of thyrotoxicosis are due to the ability of thyroid hormone to alter cardiovascular hemodynamic.[3] The usual coined terms to describe the association of thyrotoxicosis and its cardiac manifestations include "thyrotoxic heart disease", "thyro-cardiac disease" and "thyro-heart disease". Despite the frequent appearances of these terms in medical literatures, there has been no consensus of its definition. For simplicity, we may define "thyrotoxic heart disease" as the association between thyrotoxicosis and its cardiovascular complications. In this review, we briefly discuss the three cardiac consequences of thyrotoxicosis, namely atrial fibrillation, congestive cardiac failure and pulmonary hypertension.

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Received March 30, 2005; revision accepted March 31, 2005

Atrial fibrillation

Prevalence

Atrial fibrillation (AF) is the most well-known cardiovascular complication in thyrotoxic patients and its clinical importance often overshadows the most common rhythm disturbance, sinus tachycardia in this population. Atrial fibrillation occurs in 5 to 20 percent of patients with thyrotoxicosis.[4-8] On the other hands, as many as 13 percent of patients with unexplained atrial fibrillation have biochemical evidence of thyrotoxicosis.[9] In these studies, they consistently showed that the prevalence of atrial fibrillation increased with age in thyrotoxic population as in general population. Also, in one of the most frequently cited study by Sandler and Wilson published nearly half century ago, the authors observed that the prevalence of atrial fibrillation was higher among thyrotoxic men than women.[10] More recently, Shimizu et al described the prevalence of atrial fibrillation in a large cohort of 13,088 thyrotoxic patients in Ito hospital in Tokyo.[11] They showed that the annual incidence of atrial fibrillation was only 1.7%, much lower than previous studies. However, similar to previous studies, the incidence of atrial fibrillation increased with age and was higher in male thyrotoxic subjects. Unfortunately, only age and sex were analyzed in this particular study but other co-morbidities and potential confounding factors had not been adjusted.

Mechanisms

In general, for atrial fibrillation to develop, three basic components are required: 1) a specific triggers; 2) a suitable substrate; and 3) modifying factors. Haissagurere et al. have demonstrated that a single source of rapid impulses, mainly originating from the pulmonary veins,[12] is the majority source of trigger for the initiation and maintenance of AF in patients with paroxysmal AF. In thyrotoxic rat model, thyroid hormone has been shown to increase automaticity and enhance triggered activity of pulmonary vein which may increase its arrhythmogenic activity similar to that observed by Haissagurere group.[13] Besides, thyroid hormone also modifies the electrophysiological properties of the atrium: shortening the atrial action potential duration and atrial refractory period, creating substrate favor the maintenance of atrial fibrillation. In addition, modifying factors particularly autonomic tone also play contributory role in the pathogenesis of atrial fibrillation in previous studies. Both parasympathetic and sympathetic stimulation shorten the atrial refractoriness which is associated with induction and maintenance of AF.

Outcomes

It is usually assumed that successful treatment of thyrotoxicosis often associates with reversion of sinus rhythm spontaneously. However, there are only a few studies in medical literatures providing information for this issue. Nakazawa et al showed that 62% thyrotoxic patients with atrial fibrillation had spontaneous sinus conversion within the first 3 to 4 months after euthyroidism, even without anti-arrhythmic agents in 1982.[14] Also, atrial fibrillation is unlikely to revert to sinus rhythm beyond this period without cardioversion. For those thyrotoxic patients with persistent atrial fibrillation after euthyroidism achieved, DC cardioversion is highly effective for sinus conversion (~90%) and sinus rhythm maintenance rates were exceedingly high (56% at tenth year) compared to non-thyrotoxic atrial fibrillation population whom underwent cardioversion.[15]

One of the most devastating consequences of atrial fibrillation is the systemic thromboembolism including stroke. However, whether thyrotoxic atrial fibrillation population is at increased risk for systemic thromboembolism has not been clearly evaluated for the time being. Two retrospective studies, both were conducted more 15 years ago, revealed a higher embolic rate in those with atrial fibrillation than those in sinus rhythm among thyrotoxic population.[16,17] However, in one of these two studies, age rather than the presence of atrial fibrillation, was the main risk factor for thromboembolism.[16] So far, there is no large prospective population study to confirm this observation.

Congestive Cardiac Failure

Although clinical heart failure can occasionally happen in the setting of thyrotoxicosis, most patients with clinical overt heart failure are simply because of persistent sinus tachycardia or atrial fibrillation, their

left ventricular systolic function is usually normal. It is understandable that for those patients with preserved left ventricular function, the clinical congestive cardiac failure may well be secondary to rapid atrial fibrillation and possibly an element of diastolic dysfunction. However, in the setting of atrial fibrillation, the contribution of left ventricular diastolic dysfunction is rather difficult to assess. It was for many years, assumed that this condition was seen only in the presence of underlying cardiovascular disease. In recent years, occasional case reports and case series were found in medical literatures, describing thyrotoxicosis as a cause of "reversible" dilated cardiomyopathy.[18-20] However, there has been an emerging concept, introduced by Levine and his coworkers, on the basis of their clinical observations of patients in whom thyrotoxicosis was the sole or principal factor leading to clinical overt heart failure and cardiomyopathy.[21,22] However, because of the "rarity" of this clinical entity, the incidences of clinical congestive cardiac failure and dilated cardiomyopathy in thyrotoxic patients are not available in current medical literatures. In addition, their nature, prognosis and reversibility remained largely unknown.

In recent years, an enlarging body of knowledge from both human and animal studies suggesting the existence of the entity of "pure thyrotoxic dilated cardiomyopathy". Substantial body of evidence indicates that an excess thyroid hormone alone can cause cardiac failure in a number of species.[23] Forfar and associates had assessed the effects of exercise on left ventricular ejection fraction measured by radio-nucleotide ventriculography in human cases with spontaneous uncomplicated hyperthyroidism.[24] They found that in hyperthyroid state, patients exhibited a high left ventricular ejection fraction at rest but paradoxically, the EF fell significant during exercise. At the same workload and heart rate during euthyroid state, patients restored a nomal rise in left ventricular ejection fraction upon exercise. These findings suggested hyperthyroid state may result in the poor cardiac reserve despite nomal resting EF.

Changes in thyroid hormone status influence cardiac action by three different routes: 1) thyroid hormone exerts a direct effect on cardiac myocytes primarily by binding to nuclear T3 receptors influencing cardiac gene expression 2) thyroid hormone increases the sensitivity of the sympathetic system in the hyperthyroid heart and 3) thyroid hormone leads to hemodynamic alterations in the periphery which results in increased cardiac filling and modification of cardiac contraction.

Most of the molecular and cellular mechanisms responsible for cardiovascular effects by thyroid hormone exert through both genomic and nongenomic effects on cardiac myocytes (Figure 1). The genomic effects of the thyroid hormone are mediated by the transcriptional activation or repression of specific target genes that encode both structural and functional proteins. Once in the cardiac myocytes, T3 enters the nucleus and interacts with specific transcriptional activators (nuclear receptor $\alpha 1$) or repressors (nuclear receptor $\alpha 2$). Occupancy of these receptors by T3, in combination with recruited cofactors, allows the thyroid hormone-receptor complex to bind (nuclear receptor $\alpha 1$) or release (nuclear receptor $\alpha 2$) specific sequences of DNA (thyroid-responsive element, TRE), that, in turn, by acting as cis- or trans-regulators, modify the rate transcription of specific target gene.[25] Figure 1 summarized transcriptional change in difference gene expression. One example is that thyroid hormone altering the gene expression in cardiac myocytes leads to changes in the proportion of myosin heavy-chain protein from beta to alpha, thereby increasing myosin V1 and decreasing myosin V3 isozyme levels which may result in relatively ineffective use of energy in ventricular myocardium.

On the other hands, hemodynamic changes secondary to peripheral vascular effect of thyroid hormone may further complicate the picture.[6,26] As a result of thyroid hormone on the heart and peripheral vasculature, there is an increase in heart rate, blood volume, left ventricular stoke volume, ejection fraction and cardiac output. Peripheral vasodilatation occurs as a result of rapid utilization of oxygen, increased metabolic end products, and induction of arterial smooth muscle cell relaxation by thyroid hormone directly. Vasodilatation results in a decrease in systemic vascular resistance by an average of 50-60%. The decrease in systemic vascular resistance plays a central role in the hyperthyroid hemodynamic changes. Vasodilatation and lack of increase in renal blood flow cause a decrease in renal perfusion pressure and an activation of the renin-angiotensin system, thus increasing sodium reabsorption

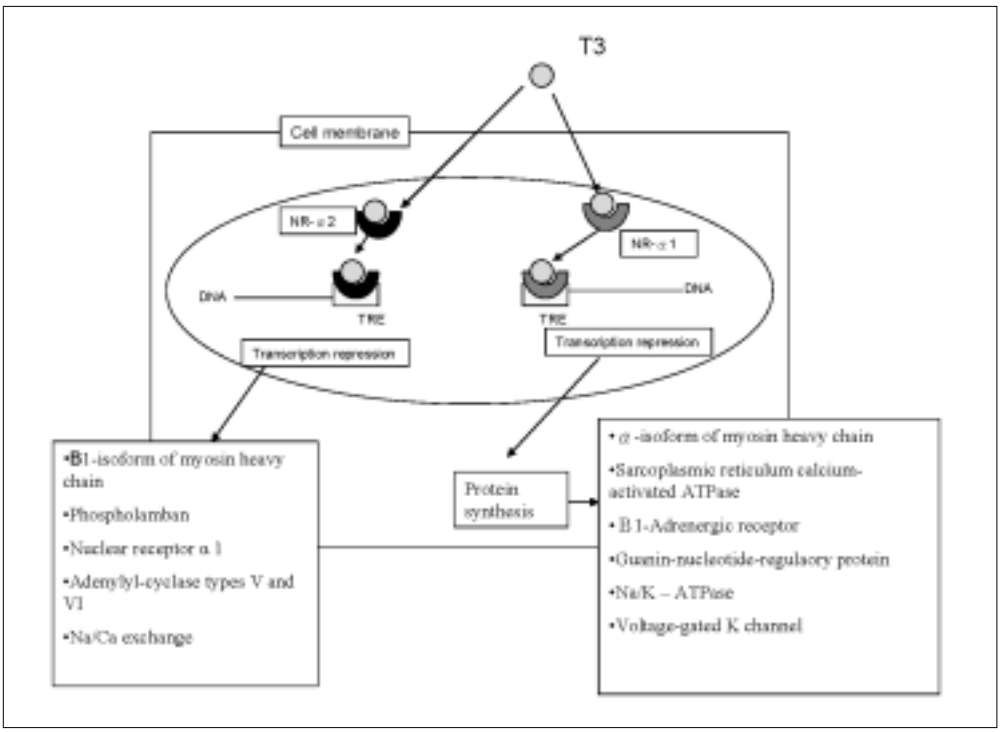

Figure 1. *Genomic effects of thyroid hormone (T3) on cardiomyocytes NR, Triiodothyronine nuclear receptor; TRE, thyroid hormone responsive element.*

and thus the blood volume. This may at the end increase the cardiac output by 2-3 folds.

It seems that in the hyperthyroid state, enormous changes in the loading situation (both pre-load and after-load) together with structural changes of the cardiac myocytes which may lead to decrease cardiac reserves, in susceptible individuals, these factors may at the end of days lead to the development of clinical overt cardiac failure in the absence of underlying heart disease.

Pulmonary Hypertension

Since early 1980s, thyrotoxicosis has been increasingly recognized as a rare cause of pulmonary hypertension as accumulating case reports and case series had been published describing this association.[27-30] In most series, pulmonary arterial hypertension were defined as the peak pulmonary systolic pressure >35 mmHg and nearly exclusively derived with echocardiographic technique. Similar to congestive cardiac failure, there has no been any large prospective population based study for this population therefore incidence, nature, prognosis and reversibility of thyrotoxic pulmonary hypertension remained largely obscure.

Two possible mechanisms have been put forwards to explain this association: 1) elevation of pulmonary vascular resistance and 2) high cardiac output in thyrotoxic state. It has been shown that there was a higher prevalence of positive anti-thyroglobulin antibody among thyrotoxic patients with isolated pulmonary hypertension (8-folds) than in the general population.[31] This observation leads to suggestion of possible autoimmune phenomenon similar to primary pulmonary hypertension, resulted in endothelial and vascular damage in thyrotoxic pulmonary hypertension. However, in the cases described by Cohen[32] and Eleftheriadis,[33] their patients presented with pulmonary hypertension and frank right heart failure, initially thought to be primary pulmonary hypertension but eventually found to be a case of thyrotoxic pulmonary hypertension. The interesting point is that in both cases, the pulmonary pressure fell back to nomal after euthyroidism achieved. This makes the possibility of autoimmune process as a cause of pulmonary vasculature damage and pulmonary

hypertension rather remote. Recently, a prospective Doppler echocardiographic study further confirmed the reversibility of pulmonary hypertension in thyrotoxicosis population.[34] In a mean follow-up time of 14±8 months, 33 thyrotoxic patients with pulmonary hypertension had significant drop in pulmonary artery systolic pressure after euthyroidism. However, it remains obscure whether the thyroid hormone exerts its effect directly on the pulmonary vasculature or the increase in cardiac output in thyrotoxic state leading to the elevation of pulmonary artery pressure, in which both may be normalized after euthyroidism.

Summary

The intimate relationship of thyroid gland and the heart can aggravate pre-existing heart disease or even lead to thyrotoxic heart diseases including atrial fibrillation, congestive cardiac failure, cardiomyopathy and pulmonary hypertension. Despite well-recognized in clinical practice, many essential clinical information including the epidemiology, outcome and management strategies, have not been fully elucidated.

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