THYROTOXICOSIS AND THE HEART [1]

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INTRODUCTION

Virtually all hormones secreted by major endocrine glands have a direct or indirect effect on the cardiovascular system; and although the precise relationship between excess thyroxin and heart disease has not been defined, thyrotoxic heart disease has been well recognized for over a century.

Parry, in 1825, first described cardiac involvement in thyrotoxicosis, consisting of palpitations, irregularity of the pulse, edema, and cardiac enlargement; more detailed descriptions by Graves and others were recorded in subsequent years.

Some writers have described thyrotoxic heart disease as a definite entity and Schlesinger and Benchimol stated that pure thyrotoxic heart disease did occur although it was a relatively uncommon condition.

Other writers, however, claimed that antecedent or concomitant primary heart disease was always present in thyrotoxic patients in whom heart disease occurred. This claim is supported by the fact that there is a progressive increase in the incidence of cardiac involvement in thyrotoxicosis with increasing age in patients with and without proven underlying heart disease. Also, it is well established that thyrotoxic heart disease is unusual prior to the age of 40, the sex distribution being similar in thyrotoxic patients with and without cardiac complication.

Younger thyrotoxic patients more commonly present evidence of catecholamine excess: tachycardia, warm flushed skin due to vasodilatation and accelerated blood flow, moist palms, and elevation of systolic and lowering of diastolic blood pressure with resultant widening of the pulse pressure. The young thyrotoxic patient usually has exophthalmos and diffuse thyroid enlargement, with a bruit over the thyroid gland. In the older patient the clinical evidence of thyrotoxicosis is commonly more subtle, he is often described as the masked hyperthyroid: unexplained atrial fibrillation, particularly when unresponsive to digitalis; unexplained sinus tachycardia; congestive heart failure without evidence of heart disease, often with a normal circulation time; congestive heart failure which responds poorly to therapy; thyrotoxic myopathy, unexplained weight loss, or episodes of alternating diarrhea and constipation. Furthermore, in the older age group the eye signs are less frequent and the thyroid gland is not as significantly enlarged as in the young patient with classic Graves's disease.

It is true that older patients with thyrotoxicosis have an increased incidence of atherosclerotic and other primary heart disease; and thus the occurrence of true thyrotoxic heart disease in the absence of underlying anatomic changes in the coronary arteries, myocardium or heart valves remains debatable. Nonetheless, it is extremely useful to examine available biochemical and hemodynamic evidence - changes that occur in the presence of excess thyroxin.

It is this sort of analysis that will help us understand the pathophysiology of thyrotoxic heart disease even in the absence of conclusive histopathologic lesions in heart muscle.

EFFECTS OF THYROID HORMONE

The metabolic effects of thyroxin are widespread and it would appear therefore that thyroxin stimulates a basic energy-producing reaction common to most tissues. There is a time lag following the administration of thyroxin before detectable changes occur, suggesting that thyroxin is not the

active form of thyroid hormone and it has been proposed that tri-idothyronine may indeed be the active form.

The metabolic action of thyroxin, in vitro, is to effect an uncoupling of oxidative phosphorylation causing wasteful heat production instead of formation of "high-energy" phosphate bonds (ATP); this may explain the hypermetabolism of hyperthyroidism. However, other substances, e.g. dinitrophenol, which actively uncouple oxidative phosphorylation and cause increased oxygen consumption cannot reproduce most effects of thyroid hormone.

At the cellular level thyroxin causes mitochondrial swelling related to alterations in mitochondrial oxidation-reduction and to ATP production. In addition, chronic thyroxin excess leads to an increase in mitochondrial numbers. A correlation can be seen between metabolic activity and mitochondrial count by comparing skeletal and cardiac muscle; the latter, which has the higher daily oxygen consumption of the two also has a much larger number of mitochondria.

Thyroxin therefore acts directly on the heart and other tissues to stimulate the metabolic rate and increase oxygen consumption; however, thyroxin depresses oxygen consumption in the anterior pituitary probably due to depression of thyrotropin synthesis and release.

Thyrotoxicosis induces a change from preponderant carbohydrate metabolism to preponderant fatty acid utilization. Normally, glucose, lactate and pyruvate etc., provide most of the energy for cardiac muscle, but no biochemical abnormality of energy liberation or conservation is evident in cardiac muscle in thyrotoxicosis, the cardiac carbohydrate metabolism is apparently normal. Thyroxin, however, inhibits enzymes which catalyze the anaerobic synthesis of high-energy phosphate compounds causing cardiac metabolism to be aerobic and thus increasing cardiac oxygen consumption.

Thyroxin excess impairs the conversion of creatine to creatinine, impairs phosphocreatine formation and produces creatinuria. CP (Creatine Phosphate) acts as a store of chemical energy and can donate its high energy phosphate group to ADP via the Lohman reaction:

$$ADP + CP \gtrless ATP + Creatine$$
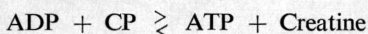
By this pathway, the store of ATP - the immediate energy source for contraction - is continually replenished by CP. Thyroxin excess significantly reduces the tension developed by myocardial muscle bundles probably reflecting creatine phosphate (CP) deficiency. Deficiency of CP causes weakness and myopathy of variable severity and the myocardium may be affected by this myopathy.

VASCULAR EFFECTS OF THYROXIN

A. The increased circulation with decreased peripheral resistance in thyrotoxicosis functionally stimulates an arteriovenous shunt and causes increased cardiac work. Arteriovenous shunting within the hyperactive goiter per se has been thought to contribute to the high output cardiac failure; however, Fowler considers the continuous murmur in the neck of thyrotoxic patients to be a cervical venous hum rather than a bruit originating in the gland itself.

B. One of the characteristic effects of the hyperthyroid state is the apparent exaggerated response to the autonomic neurohormones. On the adrenergic side, anxiety, wakefulness, tachycardia, increased contractile force of the heart, susceptibility of the heart to arrhythmias and increased systolic blood pressure all suggest hyperepinephrinism. Diarrhea and sweating suggest increased cholinergic activity, although sweating may be more closely related to heat intolerance than to potentiation of acetylcholine.

The relationship between thyroxin and epinephrine has been studied especially by Brewster et al, who found that either surgical or pharmacological blockage of the adrenergic division of the autonomic nervous system prevented the calorigenic and cardiac effects of overdosing the dog with thyroid hormone.

It is well recognized that the vascular effects of the pressor amines, epinephrine, and norepinephrine are greatly enhanced by thyroxin. Excessive thyroxin secretion increases cardiac sensitivity to sympathetic stimulation and decreases its sensitivity to vagal stimulation explaining in part the tachycardia of thyrotoxicosis. Intravenous epinephrine causes a significantly greater increase in oxygen consumption, blood pressure and heart rate in the thyrotoxic patient than in the

normal individual. Many epinephrine effects on the cardiovascular and nervous systems and on oxygen consumption are similar to the effects of thyroxin although of much shorter duration; the similarity led to the use of sympathetic blocking agents in the treatment of thyrotoxic crisis.

Thyroxin decreases epinephrine and norepinephrine degradation by inhibiting amine oxidase and/or other enzymes involved in catecholamine deactivation; epinephrine, however, cannot mimic thyroxin in action in increasing oxygen consumption in thyroidectomized animals.

HISTOPATHOLOGY OF MYOCARDIUM

Although all evidence to date refutes a specific pathologic change in the myocardium associated with thyrotoxicosis, it is worth noting some of the histopathologic changes that have been observed.

(i) Cardiac hypertrophy is uncommon in uncomplicated thyrotoxicosis; it is frequently encountered in thyrotoxic patients with atrial fibrillation and congestive heart failure and is almost invariably attributable to complicating heart disease or hypertension. It is worth noting that thyroxin sensitizes cardiac muscle to the effects of growth hormone, and this may, in part, explain the cardiac hypertrophy encountered in thyrotoxicosis. A 30 to 50 per cent incidence of cardiac enlargement has been reported in thyrotoxicosis, the most pronounced being associated with congestive heart failure usually with atrial fibrillation.

(ii) Experimental thyrotoxicosis in animals produces myofibril degeneration, myocardial edema, focal necrosis, cellular infiltration and myocardial fibrosis. Focal necrosis and interstitial myocarditis have been described. All this and many more inconclusive findings are suggestive, and certainly open up new vistas for further study. However, in the final analysis one has to look to biochemical and hemodynamic changes in order to understand the pathophysiology of heart disease in thyrotoxicosis.

CARDIOVASCULAR PATHOPHYSIOLOGY

A. As mentioned above, thyroxin excess interferes with creatine-phosphocreatine metabolism and this may in turn seriously impair the contractile ability of heart muscle. Williams reported thiamine deficiency in 75 per cent of unselected patients with thyrotoxicosis. This deficiency undoubtedly produces biochemical abnormalities in heart muscle and other tissues. The exact nature of the biochemical lesion has not been defined. There has been no conclusive report on whether there is a deficiency of co-carboxylase in heart muscle impairing its action. Meanwhile, the role of thiamine deficiency in the congestive heart failure of thyrotoxicosis remains speculative.

B. **Effects of Hypermetabolism.** Excessive amounts of thyroxin elevate the basal metabolic rate and increase the oxygen consumption. The increased tissue oxygen requirement is met by a 25 to 100 per cent increase in cardiac output. This increase in cardiac output is due primarily to increased velocity of blood flow. The rate and depth of respiration is also increased aiding the venous return of blood to the heart.

Cardiac catheterization studies in thyrotoxic patients have demonstrated an increase in cardiac output, in the left ventricular work, in coronary blood flow, and in myocardial oxygen consumption. Coronary arteriolar dilatation in thyrotoxicosis is proportional to the tachycardia and the increased cardiac work. Increased coronary blood flow is due to a decrease in cardiac output; coronary vascular resistance increases after treatment of thyrotoxicosis. Pulmonary vascular resistance remains unchanged, causing the pulmonary blood flow to increase with increase in cardiac output; there is an associated increase in systolic pressure in the right ventricle and pulmonary artery, attributable to the normal blood viscosity and absence of pulmonary vasodilatation. Myocardial hypermetabolism imposes an added burden on the increased cardiac output and cardiac work caused by the hypermetabolism of the body as a whole. The increased cardiac work required to maintain the increased peripheral blood flow is necessitated by the augmented tissue oxygen demand and by the augmented need for heat dissipation.

The increased cardiac output has been attributed to increased venous return. The increase in heat production and increase in tissue metabolites due to the elevated metabolic rate in thyrotoxicosis produce peri-

pheral vasodilatation and arteriovenous shunting. The peripheral vasodilatation with decreased peripheral resistance results in increased peripheral blood flow and increased venous return to the heart.

The increased peripheral blood flow in hyperthyroidism is obtained both by shunting of blood from the interior of the body, and by an actual increase in blood volume. The increase in blood volume correlates well with increase in cardiac output. There also occurs a significant increase in the total red cell mass, presumably in response to increased oxygen demand. The 30 to 70 per cent acceleration of circulatory velocity parallels the elevation of the basal metabolic rate and results in a diminished circulatory time.

CLINICAL FEATURES

The cardiovascular complications of hyperthyroidism are primarily those of atrial fibrillation, cardiac enlargement, and congestive heart failure; angina pectoris and disorders in rhythm are also encountered. The diagnosis of occult thyrotoxicosis has to be considered in any patient with atrial fibrillation or congestive heart failure unresponsive to the usual therapy.

In the younger patient, particularly the female, the hyperthyroidism generally presents in the more classic fashion with palpitations, moist warm skin, exophthalmos, exertional dyspnea, increased appetite, increased sweating, increased pulmonary blood flow, hyperkinetism, emotional lability; the most likely explanation for the exertional dyspnea is the thyrotoxic myopathy involving the chest wall muscles. In the older patient, the clinical manifestations may be more subtle; e.g., atrial fibrillation, congestive heart failure, palpitation and dyspnea being often the presenting complaints. Angina pectoris occurs commonly and is ascribed to increased work demand of a heart with underlying coronary atherosclerosis.

Myocardial infarction is unusual in active thyrotoxicosis but has occurred after remission of thyrotoxicosis; it may be related to elevation of serum lipid levels. The rarity of myocardial infarction may reflect the decrease in calories available for storage as fat or may be attributed to a hypolipemic effect of thyroid hormone. However, Burnstein et al have challenged the apparent nonsus-

ceptibility of thyrotoxic patients to myocardial infarction. Resting heart rate varies from 90 - 125 / min. Assessment of the sleeping pulse is important in clinically conforming the diagnosis of thyrotoxicosis and in following the patient once therapy has been instituted, as there is little reduction in the heart rate in thyrotoxicosis with sleep. Pulse is bounding as a result of increased cardiac output and peripheral vasodilatation. Most patients with thyrotoxicosis have normal sinus rhythm with a rapid heart rate. Atrial fibrillation is the only characteristic rhythmic disturbance; however, atrial flutter, nodal tachycardia, and premature contractions have been described. The systolic blood pressure in thyrotoxicosis is slightly to moderately elevated and the possible diagnosis of hyperthyroidism should be entertained in cases of unexplained systolic hypertension as hyperthyroidism appears to precipitate or exaggerate labile essential hypertension.

CONGESTIVE HEART FAILURE IN THYROTOXICOSIS

The average age at which congestive heart failure develops in thyrotoxicosis is over 50 years so that both age and co-existent cardiovascular changes are significant in the production of congestive heart failure The increased circulatory load of thyrotoxicosis causes congestive heart failure when myocardial function - both metabolic and contractile - or when the excessive circulatory load overcomes the capacity of an otherwise normal heart, and a clue suggestive of hyperthyroidism is congestive heart failure with a normal or rapid circulation time. The venous pressure usually remains normal until severe congestive heart failure develops. The increased cardiac output of thyrotoxicosis decreases somewhat with onset of congestive heart failure but often remains above normal levels.

DIAGNOSIS

(1) **Laboratory**

The laboratory diagnosis of hyperthyroidism often

(1) a. Shows slight anemia and leucopenia with relative lymphocytosis.

   b. The BMR is elevated

   c. PBI, T_4, and RAI uptake are all within hyperthyroid range.

(2) **Radiological Findings in Thyrotoxic Heart Disease**

The usual appearance of thyrotoxic heart disease in the absence of atrial fibrillation, congestive heart failure or primary heart disease is not grossly abnormal. Cardiac fluoroscopy reveals increased activity of cardiac contraction and prominence and increased pulsation of the pulmonary artery. The prominent pulmonary artery in thyrotoxicosis may straighten the left cardiac silhouette, mimicking mitral stenosis, but there is no left atrial enlargement in thyrotoxicosis in the absence of significant congestive heart failure. The pulmonary artery abnormalities regress following control of the hyperthyroidism.

(3) **Electrocardiographic Findings.** There are no distinctive electrocardiographic features of thyrotoxicosis; and the majority of the electrocardiographic abnormalities that have been described are probably associated with underlying coronary atherosclerosis, myocardial disease, or valvular heart disease rather than being specific for hyperthyroidism.

TREATMENT

The initial objective in the treatment of the thyrocardiac patient is control of the hypermetabolism. This may be achieved by the following steps:

(1) Set up an intravenous drip of 5 per cent glucose and water with 5 to 6 drops of Lugol's Iodine every 6 hours. Selenkow and others have recommended the use of liberal amounts of thiamine in order to replenish the thiamine deficiency associated with thyrotoxicosis.

(2) Adequate doses of guanethidine or reserpine are given. Either of these sympatholytic agents decreases vascular responsiveness to catecholamines as evidenced by slowing of the pulse, decrease in systolic blood pressure and narrowing of the pulse pressure.

(3) Finally, therapy of the severely ill thyrocardiac should include Tapazole (or propylthiouracyl). If Tapazole is used it may be given in doses of 10 to 15 mg. q6h.

After the thyrocardiac status has been corrected, definitive therapy of the thyrotoxicosis can be considered; and in the thyrocardiac age group it appears that I^{131} therapy is the treatment of choice.

SUMMARY

The pathophysiology and treatment of thyrotoxic heart disease has been discussed under the following theses: -

(1) As an abnormality of cellular metabolism produced by excess thyroxin.

(2) As heightened catecholamine effects on the cardiovascular system.

(3) As a high output state resulting from hypermetabolism and peripheral vascular dilatation.

Finally, in the treatment of thyrotoxic heart disease, control of hypermetabolism is the sine qua non of proper therapy.

REFERENCES

1. Hoch, F. L. *Thyrotoxicosis as a Disease of Mitochondria*, NEJM **266**: 446, 498, 1962.
2. Guyton, *"Circulatory Physiology - Cardiac Output and its Regulation"*, Saunders.
3. Paul Wood, 2nd Edition, *Diseases of the Heart and Circulation*, Eyre and Spottiswood, 1961.
4. Ciba Foundation: *Colloquia on Endocrinology*, Vol. 10, Thyroid 1957.
5. Ciba Collection, *"Endocrine System"*, Netter, 1966.
6. Ann. Int. Medicine, Vol. 64, No. 1, Pg. **81**, 1966, Morris H. Forbes, *"Neuromuscular Transmission in Thyroid Disease"*.
7. *The Heart*, Hurst and Logue, Copyright, 1966.
8. *Catecholamines*, Wurtman, Boston, NEJM, Vol. 273, No. 14, pg. 747.
9. Danowski, *Clinical Endocrinology*, Vol. 2, Thyroid, Williams and Wilkins, 1962.
10. Tata, J. R., *Intracellular and Extracellular Mechanisms for the Utilization and Action of Thyroid Hormones*, Recent Progr. Hormone Research, **18**: 221, 1962.
11. Selenkow and F. J. Marcus, *"Masked Hyperthyroidism and Heart Disease"*, Med. Clin. of North America, **44**: 1305, 1960.
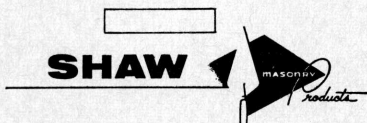
Health and life are doubtless worldly possessions of enormous value, but they are not the most valuable of human goods. Man, who wants to occupy a higher position than the beasts, must be ready to sacrifice even life and health on behalf of higher and more ideal goods.

Max Pettenkofer (1818 - 1901)

So long as there exist persons sufficiently arrogant to fancy that by speculation they will be able to achieve what the human race can only hope to achieve by strenuous labour, there will also continue to exist hypothesis which, put forward as dogmas, promise to solve all riddles at once.

Hermann von Helmholtz (1821 - 1894)