REVIEW

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Thyroid and the Heart

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ABSTRACT

Thyroid hormones modulate every component of the cardiovascular system necessary for normal cardiovascular development and function. When cardiovascular disease is present, thyroid function tests are characteristically indicated to determine if overt thyroid disorders or even subclinical dysfunction exists. As hypothyroidism, hypertension, and cardiovascular disease all increase with advancing age, monitoring of thyroid-stimulating hormone, the most sensitive test for hypothyroidism, is important in this expanding segment of our population. A better understanding of the impact of thyroid hormonal status on cardiovascular physiology will enable health care providers to make decisions about thyroid hormone evaluation and therapy in concert with evaluating and treating hypertension and cardiovascular disease. The goal of this review is to access contemporary understanding of the effects of thyroid hormones on normal cardiovascular function and the potential role of overt and subclinical hypothyroidism and hyperthyroidism in a variety of cardiovascular diseases.

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KEYWORDS: Atrial fibrillation; Cardiac output; Coronary artery disease; Heart failure; Peripheral vascular function; Thyroid dysfunction

The relationship of thyroid hormonal abnormalities and cardiovascular disease goes well beyond the risk of atherosclerosis in association with hypothyroidism and the risk of atrial fibrillation in individuals with hyperthyroidism.[1] The 2 organ systems are intimately linked by their embryological anlage, and the ubiquitous effects of thyroid hormone on the major components of the entire circulatory system: the heart, the blood vessels, and the blood, as defined by the flow law (Figure 1).[2] Cardiac output is normally modulated by peripheral arteriolar vasoconstriction and dilatation, venous capacitance, and blood volume in response to tissue metabolic needs.[3] The heart can only pump the blood that returns to it, so factors that influence venous return, such as blood volume and venous capacitance, are critical. Arteriolar dilatation reduces peripheral vascular resistance and thus, afterload, increasing cardiac output. The 4 key issues to be emphasized in this review include a discussion of the normal effects of thyroid hormone on cardiovascular function, as well as therapeutic strategies designed to manage coronary artery disease, atrial fibrillation, and heart failure when thyroid hormonal dysfunction is present. Before discussing these clinical issues, a brief summary of the thyroid hormone metabolic effects on the heart and vasculature will be reviewed.

CARDIOVASCULAR PHYSIOLOGY

In reviewing the thyroid and the circulatory system, certain key concepts are worth restating and relating to the flow law as illustrated in Figure 1. As described,[4] thyroid hormone causes myriad hemodynamic effects, and all can be related directly or indirectly to the flow law.

Thyroid function influences every structure of the heart and its specialized conducting system. Moreover,

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thyroid hormones, in addition to their direct effects on cardiovascular function, also have indirect effects mediated through the autonomic nervous system, the renin-angiotensin-aldosterone system, vascular compliance, vasoreactivity, and renal function.

THYROID HORMONE EFFECTS ON THE CARDIOVASCULAR SYSTEM

The major effects of thyroid hormones on the heart are mediated by triiodothyronine (T3) (**Figure 2**). Indeed, T3 generally increases the force and speed of systolic contraction and the speed of diastolic relaxation.[5] In addition, T3 decreases vascular resistance, including coronary vascular tone, and increases coronary arteriolar angiogenesis.[5] These multiple thyroid hormone effects are largely mediated by the action of nuclear-based thyroid hormone receptors (TR), specifically the TRα and -β. TRα is the predominant TR isoform in the heart, and it is the predominant subtype through which T3 binds to nuclear TRs and signals in cardiomyocytes.[5-8] T3-activated TR cardiomyocyte growth and maturation is mediated by phosphorylation/activation of phosphoinositol 3-kinase, protein kinase B, and mammalian target of rapamycin, which promotes a number of developmental processes, including titan (sarcomere protein) transition.[9-13] These T3-activated TR growth effects are modulated by increases in atrial natriuretic peptide and decreases in protein kinase C, especially protein kinase Cε.[11,12] T3-mediated activation of these signaling pathways initiates changes in gene expression that are compatible with the physiological cardiac hypertrophy phenotype. T3-activated TR regulates myosin heavy chain (MHC) genes, which encode for the 2 contractile protein isoforms of the thick filament of the cardiomyocyte[5-10] T3 exerts a positive effect on the transcription of the MHCα gene and a negative effect on the MHCβ gene expression (**Figure 2**).[5-10] MHC expression is modulated by T3 regulation of micro (m)-RNAs, which influence MHC mRNA turnover and translation.

Thyroid hormones can promote both physiological and pathological myocardial hypertrophy. In this regard, cardiac hypertrophy, in its initial phases, presents a physiological process that includes increased adenosine triphosphatase (ATP) and gene expression of the sarcoplasmic reticulum Ca^{2+} ($SERCa^{2+}$) and decreased expression of MHCβ (**Figure 2**). T3-activated TR cardiac effects also include the regulation of cation transport (**Figure 2**). Regulation of intracellular Ca^{2+} ($[Ca^{2+}]_i$) is important for both normal systolic and diastolic function. For example, T3 promotes increases in $SERCa^{2+}$ ATPase and the ryanodine channel, and decreases phosphorylation/activation of phospholamban, which functions to inhibit the $SERCa^{2+}$ pump.[14-18] Diastolic function of the heart is substantially influenced by the thyroid status. The speed of diastolic relaxation in the heart is markedly influenced by lowering of the $[Ca^{2+}]_i$ levels. In cardiomyocytes, most $[Ca^{2+}]_i$ lowering is achieved by pumping $[Ca^{2+}]_i$ into the sarcoplasmic reticulum by the $SERCa^{2+}$ pump. Experimental results in animal models of hypothyroidism indicate that the level and activity of the $SERCa^{2+}$ pump is markedly decreased and that of inhibitory phospholamban increased.[5] These $SERCa^{2+}$ and phospholamban changes can be linked to a decrease in the rate of diastolic relaxation. The ryanodine receptor also is decreased in hypothyroid hearts.[5] Finally, the β_1 adrenergic and the TRα receptors are positively and negatively regulated by T3, respectively, which promotes optimal modulation of T3-activated TR inotropic and chronotropic cardiac effects.[5]

CLINICAL SIGNIFICANCE

- Thyroid and cardiovascular function are intimately linked.
- When thyroid dysfunction is known or suspected, cardiovascular disease or risk should be assessed.
- When certain cardiovascular diseases, such as atrial fibrillation or sinus bradycardia occur, thyroid function should be assessed.
- Cardiac and peripheral vascular function, including cardiac and endothelial mediated vasorelaxation, is partly dependent on thyroid hormone signaling.
- Subclinical thyroid dysfunction also can be associated with cardiac disorders and merits clinical screening.

MECHANISMS OF THYROID HORMONE EFFECTS ON THE VASCULATURE

Thyroid hormones exert effects on the vasculature that generally lead to reduced vascular tone and maintenance of normal arteriolar remodeling.[5] It has been known for 2 decades that T3 exerts direct effects on vascular smooth muscle cells to promote relaxation.[5] Several mechanisms for this T3-mediated vascular relaxation have been reported. For example, it has been demonstrated that T3 dose-dependently reduces expression of the angiotensin (Ang) II type 1 receptor and reduces the increased $[Ca^{2+}]_i$ and contractile response to Ang II.[19] Further, T3 stimulates nitric oxide (NO) production via activation of the phosphoinositol 3-kinase/protein kinase B-mediated endothelial NO synthase signaling pathway.[20,21] The resulting increase in bioavailable NO is associated with decreased myosin light chain phosphorylation in response to Ang II and phenylephrine.[21] Collectively, these data suggest that T3 reduces vascular smooth muscle cell contraction by decreasing $[Ca^{2+}]_i$ as well as Ca^{2+} sensitization. Studies have shown that T3 also promotes angiogenesis and increases the density of small arterioles, including coronary arterioles.[5,22,23] This T3-activated TR effect on coronary arterioles may be especially important following myocardial ischemia and in the process of myocardial ischemic reconditioning.

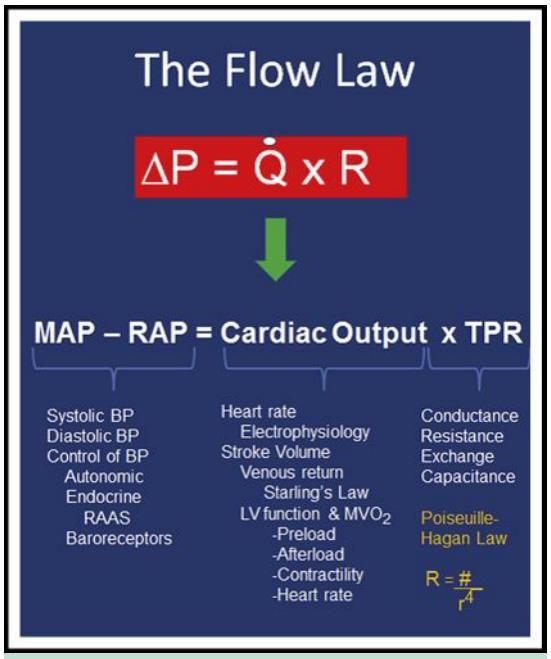

Figure 1 Each component of the flow law is influenced by thyroid hormone. MAP = mean arterial pressure; RAP = right atrial pressure; $\dot{Q}$ = cardiac output; TPR = total peripheral resistance. The Poiseuille-Hagan Law demonstrates how small changes in arteriolar radius lead to geometric changes in arteriolar resistance. R = resistance; r = radius; # = (η = dynamic fluid viscosity; ΔP = change in pressure; X = distance in direction of flow; Π = mathematical constant Pi).

THYROID HORMONES AND HEART FAILURE

The role of low thyroid hormone function in promoting heart failure and the potential benefits of thyroid hormone replacement have been reviewed extensively.[5,24] In this regard, heart failure can lead to the downregulation of the thyroid hormone signaling system in the heart.[5] In the failing heart, decreases of nuclear TR levels occur. In addition, serum levels of T4 and T3 are decreased with heart failure in the context of the nonthyroidal illness syndrome. In animal models, it can be shown that in pressure overload-induced cardiac hypertrophy, a decrease of TR levels occurs. Heart failure is an increasing medical problem in our aging population. There is increasing evidence that decreased thyroid function may contribute to systolic and diastolic dysfunction.[5,22,25] Data from clinical studies indicate that thyroid hormone replacement in patients with heart failure has beneficial effects on cardiac contractile function.[25-28] Overall, it appears that in heart failure, a hypothyroid cardiac state may occur due to decreased TR levels in failing hearts.[5,25-28] Animal studies and a limited number of human trials indicate that increasing thyroid hormone action, either by increasing T3 receptor levels or serum levels of T3 hormone itself, can improve cardiac function without significant detrimental effects.[24,29,30] It is currently unclear if long-term administration of thyroid hormone to patients in heart failure will be well tolerated and will lead to increased survival. This can only be determined by long-term randomized controlled clinical trials.

While atherosclerosis and atrial fibrillation are most commonly related to abnormal thyroid function, numerous other cardiac conditions also have been related to thyroid dysfunction. These include pericarditis, pericardial effusion,[31] cardiac tamponade, sinus bradycardia and tachycardia, atrioventricular block,[32-34] torsade de pointes ventricular tachycardia, typically with a long QTc; left ventricular systolic and diastolic dysfunction, heart failure, high output congestive state, cardiomyopathy,[35] mitral valve prolapse (in particular with autoimmune thyroid gland disorders),[36,37] endothelial dysfunction, dyslipidemia, and both systolic and diastolic hypertension.[38] Thyroid hormones exert effects on both the heart and the vascular system as discussed above. Hypothyroidism decreases endothelial-mediated vasorelaxation and vascular compliance and thus, elevated diastolic blood pressure.[39] Lowered peripheral vascular resistance in hyperthyroidism increases blood volume and venous return.[40] This can lead to what is called "high output failure" when a more accurate term is a congestive state. Clinically relevant heart failure implies that despite adequate venous return, the heart cannot pump all the blood that returns to it. However, this is not the case in uncomplicated hyperthyroidism where there is a high output state not unlike that which may occur with a peripheral arteriovenous fistula, severe anemia, pregnancy, or severe liver disease. While these cardiovascular disease abnormalities have been described with overt thyroid dysfunction, some are increasingly recognized as being associated with subclinical hypothyroidism and subclinical hyperthyroidism. Even high normal thyroid hormone function is associated with a slightly increased risk for developing atrial fibrillation.[35]

HYPOTHYROIDISM

Hypothyroidism is characterized by depressed levels of T4 and T3, with compensatory high levels of thyroid-stimulating hormone. In seeking the classic clinical manifestations of this condition such as fatigue, sluggishness, hoarse voice, constipation, delayed distal tendon reflexes, and skin changes, the clinician should also evaluate patients for cardiovascular manifestations of hypothyroidism. The most common are diastolic hypertension, sinus bradycardia due to sinus node dysfunction, and failure of the sinus node to accelerate normally under conditions of stress such as caused by fever, infection, or heart failure.[41] Other cardiac manifestations may include heart block, pericarditis, pericardial effusion, and rare cardiac tamponade.[42] Additionally, in chronic hypothyroid states there is increased risk of atherosclerosis often associated with dyslipidemia (hypercholesterolemia) and hypertension. Less common are cardiomyopathy, endocardial fibrosis, and myxomatous valvular changes.

The coronary artery disease accompanying hypothyroidism may be preexistent or be aggravated by the thyroid

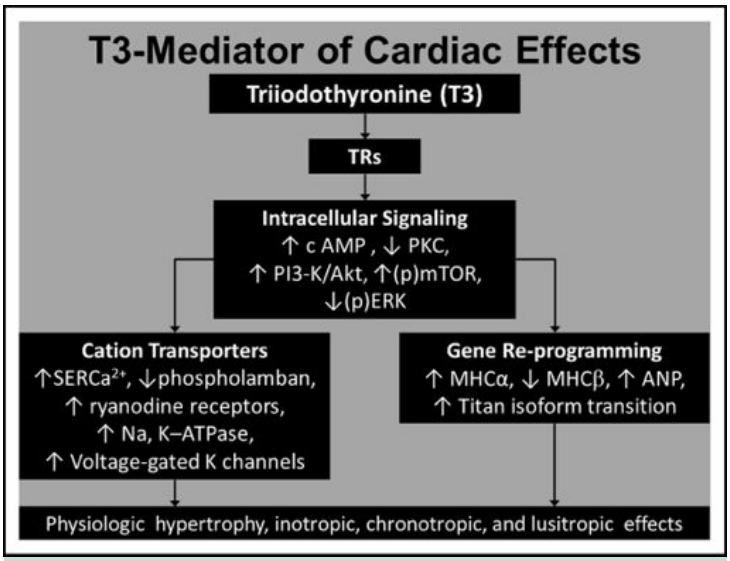

Figure 2 Thyroid hormone effects on the heart. T3 = triiodothyronine; TR = thyroid hormone receptors; cAMP = cyclic AMP; PKC = protein kinase C; PI3-K = phosphoinositol 3-kinase; Akt = protein kinase B; (p) mTOR = phosphorylation of mammalian target of rapamycin; (p)ERK = phosphorylation of extracellular-signal-regulated kinases; $SERCa^{2+}$ = sarcoplasmic reticulum Ca^{2+}; Na = sodium; K-ATPase = potassium adenosine triphosphatase; MHCα = myosin heavy chain alpha; MHCβ = myosin heavy chain alpha beta; ANP = atrial natriuretic peptide.

dysfunction, especially as peripheral vascular resistance increases. The hypertension associated with hypothyroidism may be asymptomatic or attended by overt myocardial ischemia, including angina pectoris or myocardial infarction. Great caution is needed in treating such patients with thyroid hormone replacement. The key with replacement therapy is to "go low and go slow." The apt caveat is to start with the lowest imaginable dose of thyroid hormone and cut that in half. Important exceptions are patients who are young and without coronary risk factors, or patients immediately after total thyroidectomy. There are, of course, many causes of hypothyroidism, and these will influence the judgments made about therapy. Moreover, it is particularly important to identify autoimmune thyroid disorders such as Hashimoto thyroiditis and Graves disease because these require special therapeutic considerations.

Typical electrocardiographic changes that can be seen in hypothyroidism include sinus bradycardia, a prolonged QTc (which can result in torsade de pointes ventricular tachycardia), low voltage, and the rare instance of atrioventricular block. Some of the salient cardiovascular changes that can occur when hypothyroidism is present are sinus bradycardia, decreased cardiac output, diastolic hypertension, increased myocardial oxygen demand due to increased afterload, long QTc with increased risk of torsade, increased risk of atherosclerosis due to dyslipidemia (increased total cholesterol, increased low-density lipoprotein cholesterol, decreased low-density lipoprotein receptors, hypertension, and elevated homocysteine levels), some evidence for increased abdominal aortic atherosclerosis and increased intimal-medial carotid thickening, and decreased myocardial perfusion, which can resolve with thyroid replacement therapy. Some of these changes are risk factors for coronary artery disease, some relate to the flow law, and some are prime determinants of left ventricular function and myocardial oxygen demand.

When coronary artery disease is known or suspected to be present, treating hypothyroidism is a challenge for the clinician. Key questions include: 1) What dose of thyroid replacement is best if coronary artery disease is known?, 2) What dose if coronary artery disease is suspected?, and 3) Does the patient need risk stratification for revascularization before thyroid replacement therapy is initiated? Some of the predominant pathophysiologic and therapeutic considerations with thyroid hormone replacement include the fact that there is increased maximum oxygen consumption in the setting of increased peripheral vascular resistance. Secondly, in hypothyroid patients with unstable angina, main left anterior descending coronary disease, triple vessel disease with impaired left ventricle function and with overt hypothyroidism, angioplasty or coronary artery bypass grafting, merit consideration before thyroid hormone replacement therapy. For hypothyroid patients with stable coronary artery disease, one should use lower doses of L-thyroxin and increase the dose slowly. For example, one may consider starting at 12.5 μg orally daily and increasing the dose every 6 weeks. The lowering of peripheral vascular resistance with thyroid hormone replacement also can ameliorate the

myocardial ischemia in patients with hypothyroidism. The goal of therapy is a euthyroid state with normal thyroid-stimulating hormone (TSH) and, of course, improvement in myocardial ischemia and cardiac function.

Approximately 4% of patients with hypothyroidism develop pericarditis, so the finding of pericarditis warrants checking a TSH level even if there is another obvious cause of any nontraumatic pericarditis. Patients with pericarditis require observation for effusion or tamponade although these can occur without pericarditis. The cause of pericardial effusion in hypothyroidism is not certain, but likely due to volume retention. The fluid is extruded from the surface of the heart[43] and may be golden in color due to cholesterol crystals.[44] Subclinical hypothyroidism is defined as a state with high TSH with normal blood levels of T4 and T3. Here the thyroid dysfunction is compensated for by the greater stimulation of the elevated TSH level. Despite normal levels of thyroid hormone, such patients are at somewhat increased risk of atherosclerosis. The clinical decision about starting thyroid supplement therapy will be influenced by the age of the patient, the cause of the hypothyroidism, and the presence of other atherosclerotic risk factors including hypertension and dyslipidemia. These risk factors for atherosclerosis require appropriate medical management along with thyroid supplementation. With the aging of our population and the ease of getting a TSH level, we can expect to see an increased incidence of subclinical hypothyroidism.[45] Endothelial dysfunction is a known early progenitor of hypertension and atherosclerosis. There is evidence of decreased NO-mediated vascular relaxation in patients with subclinical hypothyroidism, as demonstrated by abnormal flow-mediated vasodilatation.[46] Flow-mediated vasodilatation depends on the presence of adequate bioavailable NO in the endothelium. Evaluation of endothelial-mediated vascular relaxation has revealed reduced flow-mediated vasodilatation in individuals with subclinical hypothyroidism. Baseline and flow-mediated (NO-dependent) vasodilatation values were significantly higher in individuals with subclinical hypothyroidism after treatment with L-thyroxin. This study and another in a young cohort[47] support the notion that thyroid replacement therapy is beneficial in patients with subclinical hypothyroidism. Left and right ventricular systolic and diastolic dysfunction also have been described in subclinical hypothyroidism, and there is evidence for improvement in ventricular function with thyroid replacement therapy.[48-50]

HYPERTHYROIDISM

Hyperthyroidism is characterized biochemically by a low TSH level and elevated T4, T3, or both. The causes include Graves disease, nodular thyroid disease, and factitious or iatrogenic over dosage with thyroid hormone.[51] Patients with hyperthyroidism can develop a life-threatening complication called thyroid storm or crisis, requiring urgent therapy with beta-blockers, antithyroid medication, and iodine. This complication can be precipitated by an acute illness such as a myocardial infarction, infection, or other stress.[52] Timely treatment of this condition is especially critical in patients with underlying coronary disease or heart failure.

The clinical symptoms and signs of hyperthyroidism include systolic hypertension, increased left ventricular mass,[53] exercise intolerance, angina pectoris, and systolic murmurs.[53] Complications include atrial fibrillation with its risk of stroke, and high output and heart failure.[54,55] A serum TSH level should be measured in any patient with paroxysmal or sustained atrial fibrillation. If the TSH level is low, further thyroid evaluation is needed. Atrial fibrillation, especially in the presence of preexistent heart disease, can result in clinical heart failure. This heart failure may be due to an associated rapid ventricular response, which, when sustained, can lead to tachycardia-mediated cardiomyopathy. The loss of atrial contractile function and decreased diastolic filling time due to the tachycardia may cause increased filling pressures, further contributing to this cardiomyopathy.

Atrial fibrillation and atrial flutter management presents unique challenges in patients with associated hyperthyroidism. The usual guidelines should be followed, except that efforts to restore sinus rhythm are ordinarily delayed until the patient is euthyroid. This reduces the likelihood of the rhythm reverting to atrial fibrillation. In the absence of evidence-based studies to support anticoagulation in such patients, careful clinical judgment is required.[56] With novel anticoagulants such as the direct thrombin antagonist dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban for nonvalvular atrial fibrillation, such a decision for anticoagulant therapy is likely to be easier in the future, especially in patients who are not good candidates for warfarin.

While sinus tachycardia is the most common arrhythmia seen in hyperthyroidism, the incidence of atrial fibrillation ranges from 2% to 20%, with prevalence increasing with age. Of all cases of atrial fibrillation, only 1% is due to overt hyperthyroidism. Yet, available therapy justifies checking the TSH level in any patient with atrial fibrillation. The principle objectives in treating atrial fibrillation associated with hyperthyroidism are rate control, prevention of thromboembolism, and restoration of sinus rhythm. The following list is from the 2011 guidelines of the joint committee of the American College of Cardiology and the American Heart Association:[57] 1) Beta-blockers to control the heart rate unless specifically contraindicated; 2) When a beta-blocker cannot be used, a nondihydropyridine calcium channel antagonist is recommended; 3) Oral anticoagulation (international normalized ratio 2.0 to 3.0); 4) Once euthyroid state is achieved, antithrombotic prophylaxis is the same as for patients without hyperthyroidism.

In patients with atrial fibrillation/flutter, if digitalis is used for rate control, higher doses are typically needed. Two thirds of patients return to sinus rhythm with radioiodine or

antithyroid drugs within 2-3 months. Despite its significant iodine content, amiodarone can be used safely in these patients for rate control and cardioversion while checking the TSH level at least every 6 months. The role of new anticoagulants such as dabigatran, rivaroxaban, and apixaban remain to be determined in the patient with both atrial fibrillation and hyperthyroidism.

Using the $CHADS_2$ risk score provides useful guidelines for determining prophylactic anticoagulation and compelling considerations in the management of atrial fibrillation with regard to stroke prevention. For patients with borderline risk based on the $CHADS_2$ score, the newer CHA_2DS_2-VASc score assigns points for female sex, age 65-75 years, and vascular disease. This latter score seems to fill an important gap.

The most evidence-based study available reached variant conclusions from that discussed above[58] regarding stroke in thyrotoxic atrial fibrillation.[59] This evidence-based study involved a retrospective of 610 patients with untreated thyrotoxicosis, 91 (14.9%) of whom had atrial fibrillation, the highest frequency being in elderly patients.[59] The risk of cerebrovascular events was calculated using logistic regression methods. Only age was an important independent risk factor. The authors concluded that the indication for prophylactic treatment with anticoagulants for prevention of stroke in thyrotoxic atrial fibrillation seemed doubtful in the absence of controlled trials. Aspirin seems a good alternative in younger patients without organic heart disease. Meanwhile, the new novel anticoagulants may help resolve the issues.[60]

Heart failure in hyperthyroidism is another complex problem with many facets. It is essential to distinguish a congestive state from clinical heart failure. If heart failure exists, a number of conditions can precipitate it. Adding a Doppler echocardiogram to a careful history and physical will usually clarify if structural heart disease or dysfunction is present. The differential diagnosis of heart failure, with which the Doppler echocardiogram can assist, includes high output failure (congestive state), tachycardia-induced cardiomyopathy, precipitation by atrial fibrillation, precipitation by coexistent organic heart disease including coronary heart disease, hypertension, valvular disease including mitral valve prolapse, left ventricular dilatation leading to mitral regurgitation, and ruling out cardiac tamponade.

The presence of hyperthyroidism does not exclude other common causes of heart failure. Moreover, there is an essential basic principle that applies: whenever an organ or organ system fails, look for a precipitating cause. Common causes of heart failure include onset of atrial fibrillation, uncontrolled ventricular response with atrial fibrillation, uncontrolled hypertension, excessive salt intake, failure to adhere to medical therapy, myocardial ischemia or infarction, papillary muscle dysfunction, ruptured chordae, endocarditis, other infections, renal failure, and of course, hyperthyroidism. In 2009 the Food and Drug Administration approved the Thyretain TSI Reporter Bioassay (Quidel Corporation, San Diego, Calif), the first test specifically detecting thyroid-stimulating immunoglobulin (TSI), the causative agent for Graves disease. Initial testing includes a TSH, T3, and FT4 in asymptomatic or symptomatic patients at clinically increased risk of hyperthyroidism. If the TSH is low or even borderline low, step 2 is to repeat the TSH to confirm accuracy, and obtain TSI and thyroid peroxidase antibody tests. If the TSI test is negative, but TSH, T3, or FT4 are abnormal, the clinician should pursue further cardiovascular work-up and consider consultation with an endocrinologist.

When hyperthyroidism is suspected in a patient with atrial fibrillation, the TSI test should be obtained, and attempts to restore sinus rhythm should be deferred until the patient is rendered euthyroid in order to reduce the risk of failure to convert, or of recurrent atrial fibrillation. Beta-blockers have a preeminent role in the management of heart failure in hyperthyroidism, although the ultimate treatment is restoration of a euthyroid state.

Subclinical hyperthyroidism is defined as normal T4 and T3 levels, with a low TSH level. As with subclinical hypothyroidism, the ease of getting TSH levels results in an increased recognition of subclinical hyperthyroidism, especially in the elderly. Such patients also have an increased risk of developing atrial fibrillation. Indeed, the Rotterdam study showed that even individuals with high normal thyroid function (high range of normal TSH levels) have an increased such risk, as well as for atherosclerosis and myocardial infarction in elderly women.[61-63] Such patients require periodic monitoring to search for evidence of overt hyperthyroidism. A decision to treat subclinical hyperthyroidism depends on its cause, evidence of cardiac disease, and comorbidities.

While controversy remains for the management of both subclinical hyperthyroidism and hypothyroidism, it was concluded in a recent review[51] that a clinical decision about initiating therapy requires consideration of the cause of the thyroid disease, the degree of thyroid function tests abnormality, associated comorbidities, risk of progression, age of the patient, and coexistent conditions such as pregnancy. The authors recommend the urgent need for large-scale randomized trials. Meanwhile, investigators[64] using data from 10 prospective cohort studies totaling 52,674 patients assessed the risks of coronary heart disease mortality and events and atrial fibrillation in patients with subclinical hyperthyroidism and concluded that risks were increased when the TSH level was lower than 0.10 mU/L. In this regard, most patients with both primary hypothyroidism and Graves disease will have positive antibodies, as iterated in 2 review articles.[65,66]

CONCLUSION

Thyroid hormone affects virtually every anatomic and physiologic component of the cardiovascular system. In the presence of heart disease, pericardial disease, heart failure, or arrhythmias, overt or subclinical thyroid dysfunction merits a high level of clinical suspicion. The ease of

obtaining a screening TSH level, especially in our aging population, means many more patients will need assessment, risk stratification, and treatment in the future. By understanding pertinent cardiovascular physiology and pathophysiology, physicians will have a firmer basis for making the often-complicated recommendations for patient care even when evidence-based studies are not yet available. Meanwhile, for subclinical thyroid disease, while routine treatment remains controversial, routine screening with TSH levels merits implementation, especially in pregnant women, women over 60 years of age, and anyone whose risk of thyroid dysfunction is high.[67]

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