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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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.