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REVIEW ARTICLE

Effects of thyroid hormones on the heart

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Abstract Thyroid hormones have a significant impact on heart function, mediated by genomic and non-genomic effects. Consequently, thyroid hormone deficiencies, as well as excesses, are expected to result in profound changes in cardiac function regulation and cardiovascular hemodynamics. Thyroid hormones upregulate the expression of the sarcoplasmic reticulum calcium-activated ATPase and downregulate the expression of phospholamban. Overall, hyperthyroidism is characterized by an increase in resting heart rate, blood volume, stroke volume, myocardial contractility, and ejection fraction. The development of ''high-output heart failure'' in hyperthyroidism may be due to ''tachycardia-mediated cardiomyopathy''. On the other hand, in a hypothyroid state, thyroid hormone deficiency results in lower heart rate and weakening of myocardial contraction and relaxation, with prolonged systolic and early diastolic times. Cardiac preload is decreased due to impaired diastolic function. Cardiac afterload is increased, and chronotropic and inotropic functions are reduced. Subclinical thyroid dysfunction is relatively common in patients over 65 years of age. In general, subclinical hypothyroidism increases the risk of coronary heart disease (CHD) mortality and CHD events, but not of total mortality. The risk of CHD mortality and atrial fibrillation (but not other outcomes) in subclinical hyperthyroidism is higher among patients with very low levels of thyrotropin. Finally, medications such as amiodarone may induce hypothyroidism (mediated by the Wolff–Chaikoff), as well as hyperthyroidism (mediated by the Jod–Basedow effect). In both instances, the underlying cause is the high concentration of iodine in this medication.

Abbreviations: AIH, amiodarone-induced hypothyroidism; AIT, amiodarone-induced thyrotoxicosis; AF, atrial fibrillation; ANP, atrial natriuretic peptide; CHD, coronary heart disease; T2, diiodothyronine; LV, left ventricular; RAAS, Renin–Angiotensin–Aldosterone system; rT3, reverse T3; SHyper, subclinical hyperthyroidism; SHypo, subclinical hypothyroidism; SCTD, subclinical thyroid dysfunction; TMC, tachycardia-mediated cardiomyopathy; TRs, thyroid hormone receptors; TREs, thyroid hormone response elements; TH, thyroid hormones; TSH, thyroid stimulating hormone; TRH, thyrotropin-releasing hormone; T4, thyroxine; T3, triiodothyronine.

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PALABRAS CLAVE
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Efectos de las hormomas tiroideas en el corazón

Resumen Las Hormonas Tiroideas (HT) tienen un impacto significativo sobre la función cardiaca, el cual es mediado por efectos genómicos y no-genómicos. Como consecuencia, la deficiencia y el exceso de las HT origina profundos cambios en la regulación de la función cardiaca y en algunos aspectos hemodinámicos y cardiovasculares. Las HT supra-regulan la expresión de la ATPasa activada por calcio del retículo sarcoplasmático, e infra-regulan la expresión de fosfolambán. En general, el hipertiroidismo se caracteriza por un incremento en la frecuencia cardiaca en reposo, del volumen sanguíneo, de la contractilidad miocárdica y del volumen sistólico, entre otros. El desarrollo de ''Falla cardiaca de alto gasto'' en hipertiroidismo puede ser debido a ''Cardiomiopatía mediada por taquicardia''. Por otro lado; en el estado hipotiroideo, la deficiencia de HT origina bradicardia, debilidad en la contractilidad y relajación miocárdica, con prolongación del tiempo sistólico y diastólico temprano. La disminución en la precarga se debe a las alteraciones en la función diastólica; la post-carga se incrementa, y las funciones cronotrópicas e inotrópicas están disminuidas. El hipotiroidismo subclínico incrementa el riesgo de mortalidad por Enfermedad Arterial Coronaria (EAC) y de eventos por EAC, pero no aumenta el riesgo de mortalidad total. El riesgo de mortalidad por EAC y de fibrilación auricular (pero no de otros resultados) en hipertiroidismo subclínico es mayor entre pacientes con niveles muy bajos de tirotropina. Finalmente, medicamentos como la amiodarona puede inducir hipotiroidismo (mediado por el efecto de Wolff-Chaikoff, además de hipertiroidismo (mediado por el efecto de Jod-Basedow. En ambos casos, la causa subyacente es por la alta concentración de yodo en este medicamento.

Introduction

It is likely that all cells in the body are targets for thyroid hormones (TH). Despite not being strictly necessary for life, TH have profound effects on many physiologic processes. Changes in thyroid status markedly influence cardiac contractile and electrical activity; increased or reduced action of TH on certain molecular pathways in the heart and vasculature causes relevant cardiovascular derangements. Receptors for TH are intracellular DNA-binding proteins that function as hormone-responsive transcription factors; TH enter cells through membrane transporter proteins. A number of plasma membrane transporters have been identified, some of which require ATP hydrolysis; once inside the nucleus, the hormone binds to its receptor, and the hormone-receptor complex interacts with specific DNA sequences in the promoter regions of responsive genes. The effect of DNA-binding of the hormone-receptor complex is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes. Cellular actions of TH may be initiated within the cell nucleus, at the plasma membrane, in cytoplasm and cytoskeleton, and in organelles; changes in gene expression caused by TH have a significant effect on the contractile apparatus and the sarcoplasmic reticulum. Consequently, it is expected that TH excess or deficit will be reflected in increased myocardial contractility, heart rate, relaxation, arrhythmias and cardiac output (in hyperthyroidism), and decreases in these parameters in hypothyroidism.

Thyroid hormone nuclear receptors (TRs) mediate the biological activities of T3 via transcriptional regulation, and the genes that are transcriptionally regulated by T3 are critical in the regulation of systolic and diastolic properties of the myocardium. T3 is the biologically active thyroid hormone; it is mostly generated peripherally by 5′-monodeiodination of thyroxine (T4). TH have a pro-angiogenic effect in adults and can stimulate arteriolar growth in the normal heart as well as after myocardial infarction. In presence of hyperthyroidism, the preload is increased; there is high cardiac output, with increased heart rate, reduced peripheral vascular resistance and hyperdynamic circulation. The reduction in systemic vascular resistance is responsible for the decrease in renal perfusion pressure and for activation of the Renin–Angiotensin–Aldosterone system (RAAS), with the resulting increase in sodium absorption and blood volume. The increased risk of cardiac mortality could be a consequence of the increased risk of arrhythmias, especially atrial fibrillation (AF), and the risk of heart failure in these subjects. In presence of hypothyroidism, there are important changes in cardiac structure and function, with severity depending on the degree and the duration of TH deficiency. This state is characterized by low cardiac output, decreased heart rate and stroke volume, reduction in systolic and diastolic functions; there is also a decline in cardiac preload and blood volume, as well as a drop in renal perfusion with impaired free water clearance and hyponatremia. The low cardiac output is caused by bradycardia and a reduction in ventricular filling and cardiac contractility. Systemic vascular resistance may increase, and diastolic relaxation and filling are slow. An increase in cardiovascular risk and mortality has also been described.