

Thyroid, aldosterone, and cardiovascular disease

Charalambos Vlachopoulos, MD; Dimitrios Terentes-Printzios, MD
Hypertension Unit and Peripheral Vessels Unit, First Department of Cardiology, Athens Medical School,
Hippokration Hospital, Athens, Greece

Correspondence: Charalambos Vlachopoulos, MD, 24 Profiti Elia str, Athens 14575, Greece
E-mail: cvlachop@otenet.gr

Abstract

The endocrine and cardiovascular systems have essential pathophysiological links. As expected, dysfunction of one leads to harmful consequences to the other. Thyroid hormones and aldosterone are two examples of this close association. Dysfunction of the thyroid gland is usually suspected due to cardiovascular symptoms, such as those related to increased blood pressure and rhythm disturbances. Thyrotropin, also known as thyroid-stimulating hormone, is the initial screening test used. Importantly, even subclinical forms of thyroid dysfunction can affect cardiovascular prognosis. Similarly, increased levels of aldosterone are implicated in several cardiovascular disorders, such as hypertension and heart failure. Blockade of aldosterone in these conditions leads to improved prognosis. Contrary to some other chronic diseases, endocrine dysfunction can be reversed or at least adequately managed in order to improve cardiovascular health and reduce cardiovascular events. For these reasons, it is of paramount importance for the cardiologist to work hand in hand with the endocrinologist in such patients. ■ *Heart Metab.* 2015;66:3-6

Keywords: aldosterone; cardiovascular disease; heart failure; hormone; thyroid

Endocrine function is a cornerstone in both cardiovascular physiology and cardiovascular disease.¹ As expected, endocrine disorders, either in the form of overt hypofunction/hyperfunction or even in their subclinical form, have essential effects on the cardiovascular system. Two endocrine glands associated mostly with cardiovascular physiology are the thyroid and the adrenal gland. There is a large number of clinical studies that have explored the effect of these two glands and their secreted hormones on cardiovascular health. The scope of this review is to investigate the main cardiovascular alterations that are related to the thyroid hormones and aldosterone in cases of endocrine dysfunction. Additionally, we comment on the cardiovascular therapeutic

opportunities offered by these hormones for improvement of cardiovascular health and prognosis.

Thyroid and cardiovascular disease

Thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), are produced in the thyroid gland in a molar ratio of approximately 1 to 7. Every enzymatic step in the synthesis and secretion of T_4 and T_3 is regulated by thyrotropin, also known as thyroid-stimulating hormone (TSH). The TSH test is the appropriate initial screening for thyroid dysfunction in several cardiovascular clinical entities and risk factors known to be affected by thyroid disease such as hypertension, atrial fibrillation, and dyslipidemia.²

Abbreviations

ARR: aldosterone-to-renin ratio; **RAAS:** renin-angiotensin-aldosterone system; **T₃:** triiodothyronine; **T₄:** thyroxine; **TSH:** thyrotropin/thyroid-stimulating hormone

The effects of thyroid hormones on the cardiovascular system are the most clinically useful and sensitive signs of thyroid dysfunction. Regarding pathophysiology, thyroid dysfunction has essential cardiovascular consequences in myocardial contractility, peripheral hemodynamics, and heart rate (Figure 1).² Thyroid

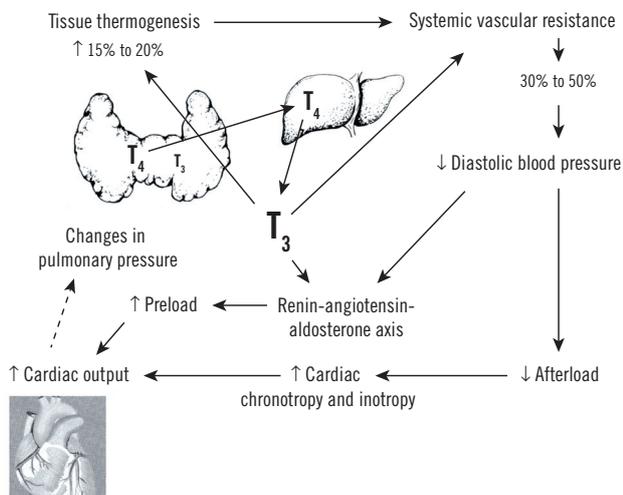


Fig. 1 Effects of thyroid hormones on cardiovascular function. **Abbreviations:** T₃, triiodothyronine; T₄, thyroxine. **Modified from reference 2:** Danzi et al. Med Clin North Am. 2012;96(2):257-268. © Elsevier Inc.

hormones, in addition to their direct effects on cardiovascular function, also have indirect effects mediated through the autonomic nervous system, renin-angiotensin-aldosterone system (RAAS), and renal function, and resultant changes in vasoreactivity, arterial stiffness, and atherosclerosis.³ The importance of vascular function and especially aortic stiffness as assessed by pulse wave velocity is high, as arterial stiffness is an independent and strong predictor of cardiovascular prognosis and all-cause mortality.^{4,5}

Hyperthyroidism

Cardiovascular symptoms are often the principal clinical elements of patients with hyperthyroidism. Palpitations are common in most patients, resulting from increases in cardiac contractility. Heart rate increase is caused by an increase in sympathetic tone and a decrease in parasympathetic stimulation. Heart rate

increase during exercise is exaggerated. Many patients with hyperthyroidism experience exercise intolerance and exertional dyspnea.

Systolic hypertension is common in hyperthyroid patients. This elevation in systolic pressure may result from the combined effect of increased preload and cardiac output, as well as of increased arterial stiffness. Consequently, left ventricular hypertrophy has been associated with the hyperthyroid state. Furthermore, in the long term, hyperthyroidism is also associated with diastolic dysfunction. In severe, untreated cases, it may even lead to heart failure.⁶ Increased rates of pulmonary hypertension have been observed in hyperthyroidism.

Sinus tachycardia is the most common rhythm alteration in patients with hyperthyroidism. However, atrial fibrillation is the most clinically important arrhythmia of hyperthyroidism. The prevalence of atrial fibrillation ranges from 2% to 20% and increases progressively with age. Symptomatic treatment of atrial fibrillation includes β-blockers that can rapidly alleviate symptoms of hyperthyroidism in contrast to the mainstay treatment for hyperthyroidism that requires a longer period of time to restore the euthyroid state. Anticoagulation in patients with hyperthyroidism and atrial fibrillation is controversial.

A small percentage of hyperthyroid patients can present with angina-like chest pain that could imply myocardial ischemia due to increase in cardiac work or even a form of vasospastic angina. Even in its subclinical form, hyperthyroidism is associated with an increased risk of coronary heart disease events and mortality, especially when levels of TSH are below 0.10 mIU/L.⁷

Hypothyroidism

The cardiovascular features of hypothyroidism are more subtle and less conspicuous. Bradycardia, diastolic hypertension, and narrow pulse pressure are all typical. Changes in cardiovascular function and hemodynamics caused by hypothyroidism are entirely opposite to those of hyperthyroidism (Table 1).² Furthermore, hypothyroidism also produces increases in total cholesterol and low-density lipoprotein cholesterol analogous to the rise in TSH level. The serum creatine kinase level is substantially elevated in up to 1 out of 3 patients with hypothyroidism. Pericardial effusion may also be a consequence of hypo-

thyroidism. Plausible mechanisms are a decrease in lymphatic clearance function and an increase in the volume of distribution of albumin. Prolongation of QT interval can also be observed.

As expected, exacerbation of cardiovascular risk factors, such as hypertension, hypercholesterolemia, and increased homocysteine, with hypothyroidism can lead to atherosclerosis and eventually overt cardiovascular disease. Hypothyroidism, even in the form of a subclinical condition, is associated with coronary heart disease events and mortality, particularly in those patients with a TSH concentration of 10 mIU/L or greater.⁸

Hormone replacement treatment with levothyroxine in patients older than 50 years with known or suspected coronary artery disease should be cautiously initiated following the combined assessment by both a cardiologist and an endocrinologist.

Aldosterone and cardiovascular disease

Aldosterone is a mineralocorticoid hormone that is produced from cholesterol in the zona glomerulosa of the adrenal cortex by a series of enzymatic reactions.⁹ The RAAS regulates aldosterone synthesis mainly by angiotensin II, which binds to the angiotensin II type I receptor on cells of the zona glomerulosa. Other regulatory factors include serum sodium and potassium levels and adrenocorticotrophic hormone. Mineralocorticoid hormones work to maintain normal sodium and potassium concentrations, and to maintain normal volume status. Renin secretion responds principally to changes in intravascular volume.

Hyperaldosteronism

Primary hyperaldosteronism is a group of clinical entities in which aldosterone production is disproportionately high, resulting in inhibition of the RAAS.⁹ Hypertension is the hallmark clinical characteristic of hyperaldosteronism.¹⁰ The prevalence of hyperaldosteronism is reported as up to 1% to 5% of patients with hypertension, and 5% to 20% of patients with resistant hypertension.¹ Potassium depletion is also a hallmark of hyperaldosteronism. Screening for hyperaldosteronism is made by measuring plasma aldosterone and plasma renin activity, and calculating an aldosterone-to-renin ratio (ARR). Patients with a positive ARR (ARR >20 with aldosterone >15 ng/dL) should be further evaluated.

Hyperaldosteronism causes pathologic cardiac remodeling and has been implicated in left ventricular hypertrophy, diastolic dysfunction, and cardiac fibrosis. Increased aldosterone levels have been shown to cause endothelial dysfunction and promote inflammation, while aldosterone-mediated vascular fibrosis leads to increased arterial stiffness. Finally, hyperaldosteronism has been associated with impaired glucose tolerance and decreased insulin sensitivity. These deleterious effects could partly explain the detrimental effect of primary aldosteronism on cardiovascular mortality, even in treated patients.¹¹

In myocardial infarction and heart failure, aldosterone levels are elevated and contribute to maladaptive cardiovascular remodeling via direct effects on collagen deposition and consequential cardiovascu-

Measurements, signs, and symptoms	Normal	Hyperthyroid	Hypothyroid
<i>Hemodynamics</i>			
Isovolumic relaxation time (ms)	60-80	25-40	>80
Heart rate (bpm)	72-84	88-130	60-80
Cardiac output (L/min)	5.8	>7.0	<4.5
Blood volume (% of normal)	100	105.5	84.5
Systemic vascular resistance (dyn•s•cm ⁻⁵)	1500-1700	700-1200	2100-2700
<i>Signs, symptoms, findings of tests</i>		Palpitations, atrial fibrillation	Bradycardia
		Anginal chest pain	Increased serum cholesterol
		Exercise intolerance, exertional dyspnea	Decreased endurance, fatigue
		Systolic hypertension, cardiac hypertrophy, pulmonary hypertension, heart failure	Impaired cardiac contractility, impaired diastolic function

Table 1 Cardiovascular symptoms, signs, and hemodynamics in different thyroid states.

Abbreviations: ms, milliseconds; bpm, beats per minute.

Modified from reference 2: Danzi et al. Med Clin North Am. 2012;96(2):257-268. © Elsevier Inc.

lar fibrosis. Many studies have shown that aldosterone blockade ameliorates these deleterious effects. Two large randomized clinical studies, the Randomized Aldactone Evaluation Study (RALES) and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), confirmed the beneficial effect of aldosterone blockade and introduced aldosterone antagonists in the treatment of heart failure.¹² However, the beneficial effects of aldosterone blockade in diastolic dysfunction and heart failure are controversial and probably minimal.¹³ Finally, despite the fact that studies have shown a beneficial effect of mineralocorticoid receptor blockade when added to standard therapy on proteinuria in patients with diabetic nephropathy, hyperkalemia still remains an important issue.¹⁴

Conclusion

Both thyroid hormones and aldosterone have essential effects on the cardiovascular system. Imbalance of their levels leads to disturbance in the homeostasis of the cardiovascular system. Importantly, most of these deleterious hormone-mediated cardiovascular effects can be reversed or managed with the proper regulation or blockade of these hormones. Therefore, it is important for both endocrinologists and cardiologists to apply a global approach in the assessment of such patients. ■

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