Review Article

The Heart of the Matter: Cardiac Manifestations of Endocrine Disease

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Abstract

Endocrine disorders manifest as a disturbance in the milieu of multiple organ systems. The cardiovascular system may be directly affected or alter its function to maintain the state of homeostasis. In this article, we aim to review the pathophysiology, diagnosis, clinical features and management of cardiac manifestations of various endocrine disorders.

Keywords: Cardiovascular disease, endocrine disorders, hypothyroidism, pheochromocytoma

Introduction

Hormonal excess or deficiency results in disease states through interactions with multiple organ systems. Endocrine disorders may result in cardiovascular alterations in response to perceived changes in homeostasis. In this review, we shall strive to address various cardiac manifestations secondary to endocrine dysfunction and the benefits of correcting them. The association between diabetes mellitus and cardiovascular disease is well known and has been elaborately studied in other sources. Hence, this aspect has been excluded from this review.

Thyroid Gland

Thyroid hormones exert positive chronotropic and inotropic effects on the heart. The state of hyper and hypothyroidism has an adverse impact on the cardiovascular system, especially when left untreated.

Hypothyroidism

Hypothyroidism is associated with cardiovascular manifestations such as increased systemic vascular resistance (SVR), normal or reduced resting heart rate, reduced cardiac contractility, raised diastolic pressure, a narrowed pulse pressure, and decreased cardiac output.[1] The cardiac output may decrease by as much as 30%–40% secondary to a reduction in the stroke volume and heart rate.[2] Triiodothyronine (T_3), the biologically active form of thyroid hormone, regulates multiple structural and regulatory myocyte genes related to cardiac contractile function at the genetic level, such as sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA2), phospholamban (an integral SR protein that regulates SERCA2 activity), and α and β myosin heavy chains (MHC). SERCA2 and α-MHC are positively regulated whereas phospholamban and β-MHC are negatively regulated by T_3.

T_3 regulates multiple myocardial plasma membrane ion transporters (e.g., Na^+/K^+ ATPase, Na^+/Ca^{2+} exchanger, and voltage-gated potassium channels like Kv1.5 and Kv4.2).[3] T_3 plays a role in reducing SVR by direct effects on vascular smooth muscle cells (VSMCs) and by effecting changes in vascular endothelium by stimulation of synthesis and secretion of nitric oxide (NO). Overt hypothyroidism induces changes in atherosclerotic risk factors such as hypercholesterolemia, increased carotid intimal medial thickness (IMT), and reduced production of endothelial-derived NO.[4] Hyperlipidemia is due to decreased expression of hepatic low-density lipoprotein (LDL) receptors and reduced cholesterol clearance. The activity of cholesterol α-monooxygenase, which mediates breakdown of cholesterol, is also reduced.[2] Pericardial effusions occur in up to 25% of patients with hypothyroidism

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and are likely due to increased capillary permeability, increased volume of distribution of albumin, and impaired lymphatic drainage.[1]

Hyperthyroidism

Cardiovascular manifestations of hyperthyroidism include palpitations, exercise intolerance, exertional dyspnea, systolic hypertension, and widening of pulse pressure. Electrocardiogram (ECG) may show sinus tachycardia, atrial fibrillation, atrial and ventricular premature beats. Sinus tachycardia may progress to atrial fibrillation in 5%–15% of patients with overt hyperthyroidism. Approximately 60% of these patients revert back to sinus rhythm with attainment of a euthyroid state.[5]

Other features include decreased SVR, increased heart rate, cardiac output, preload, and cardiac contractility. The decrease in SVR is caused by thyroid hormone-mediated vascular smooth muscle relaxation and endothelial NO production. The reduced SVR triggers an activation of the renin-angiotensin-aldosterone system causing an increased plasma volume and preload. Upregulation of erythropoietin secretion by thyroid hormones results in an increase in circulating blood volume increasing cardiac preload.[4] The net result of the increase in cardiac contractility, heart rate, increased circulatory volume, and decreased SVR is an elevated cardiac output which ranges from 50% to 300% more than normal. The resultant left ventricular hypertrophy (LVH) in association with arrhythmias such as atrial fibrillation leads on to symptoms and signs of congestive cardiac failure.[6]

Pulmonary arterial hypertension (PAH) has a prevalence of 43% in overt hyperthyroidism.[7] One of the proposed mechanisms includes an increase in pulmonary arterial pressures secondary to the LV failure, and hyperdynamic circulation. Thyroid hormones bind to integrin $\alpha_v\beta_3$ and fibroblast growth factor receptors, stimulating endothelial cell proliferation and angiogenesis leading on to PAH. These changes can be offset and normalized by the treatment of hyperthyroidism and attaining a euthyroid state.[8]

Amiodarone

Amiodarone is a benzofuran iodine rich anti-arrhythmic drug. A unique trait of this drug is its efficacy in the management of cardiac arrhythmias, but it simultaneously poses an independent risk to cardiac function, by causing either hyper or hypothyroidism. It causes thyroid dysfunction in about 15%–20% of patients undergoing treatment. The effects of amiodarone (containing 37% by weight of iodine) on the thyroid gland and thyroid function are secondary to either a direct effect on the thyroid or indirectly through multiple immunologic responses.[9]

As amiodarone and thyroid hormones are structurally similar, it can act at many cells and organs as a thyroid hormone analog. Amiodarone also reduces the activity of hypothalamic thyrotropin-releasing hormone and pituitary 5'-monodeiodinase Type-2 (D2).[10] Amiodarone is dealkylated to desethylamiodarone (DEA) in the liver. DEA acts as a TR-α1 and -ß1 receptor antagonist. As amiodarone is lipophilic, it concentrates in various tissues such as the adipose tissue. As a result, amiodarone and DEA have long half-lives (40 and 57 days, respectively).[11] Amiodarone also inhibits thyroid hormone uptake into peripheral tissues and D2 activity (responsible for the conversion of T_4 to T_3) which results in a rise in T_4 and fall in T_3.[12]

Amiodarone-induced hypothyroidism (AIH) results from persistent iodine-induced inhibition of thyroid function. This inhibition is more prevalent in patients with preexisting autoimmune thyroid disease. AIH is managed by supplementation of high doses of T_4 as amiodarone decreases deiodinase activity resulting in decreased conversion of T_4 to the active form T_3.[13]

Amiodarone-induced thyrotoxicosis (AIT) occurs in about 2%–10% of patients and is of two forms – Type-1 AIT (iodine-induced hyperthyroidism) or Type-2 AIT (destructive thyroiditis). Type-1 AIT is managed with antithyroid drugs and occasionally potassium perchlorate. Type-2 AIT is managed with glucocorticoids, beta blockade, and on rare occasions, a thyroidectomy too may be indicated.[14]

The Parathyroid Gland

Primary hyperparathyroidism (PHPT) is usually due to a parathyroid adenoma or a parathyroid hyperplasia with an elevated or high normal calcium levels. Secondary hyperparathyroidism results from chronic kidney disease or vitamin D deficiency. The most common cause for hypoparathyroidism is inadvertent removal of parathyroid glands following thyroidectomy or extensive neck dissection or after surgery for PHPT which has hypocalcemia as a main feature. Chronic hypocalcemia rather than acute hypocalcemia may have an adverse impact on cardiovascular system.[15]

Hyperparathyroidism

Serum PTH levels may be predictive of coronary heart disease[16] and may have a direct action on vasculature causing alterations in blood pressure (BP), increased intimal wall thickness, and carotid wall stiffness in hypercalcemic PHPT patients.[17] Postulated mechanisms include a stimulatory effect of PTH on VSMCs that could be secondary to PTH-mediated calcium influx into VSMCs[18] causing contraction and increase in peripheral resistance. Other mechanisms include direct PTH-mediated stimulation of the renin-aldosterone system, endothelial dysfunction, and elevated sympathetic activity. An increase in total collagen synthesis and reorganization of collagen I increases vascular stiffness.[19] These changes result in hypertension which does not usually reverse with excision of parathyroid adenomas.[20]

The trophic effect of PTH on cardiomyocytes causes hypertrophy of the cells. Surgical correction of hyperparathyroidism may result in regression of LVH in some studies. Diastolic dysfunction with a reduced E/A (ratio of peak velocity flow in early diastole [the E wave] to peak velocity flow in late

diastole caused by atrial contraction [the A wave]) ratio, and prolonged isovolumetric relaxation time has also been noted in moderate-to-severe PHPT. Calcifications may occur in the myocardium, aortic, and mitral valves in PHPT patients with severe hypercalcemia.[21]

Hypoparathyroidism

Cardiovascular manifestations in hypoparathyroidism are usually secondary to the resultant hypocalcemia leading to QT interval prolongation, cardiac arrhythmias, heart failure, and reduced LV ejection fraction (LVEF). Extracellular calcium is needed for myocardial contraction due to the inability of the SR to sequester sufficient calcium ions to initiate contraction. Hence, a supplemental extracellular source of calcium ions is required.[22] A key feature of cardiovascular effects of hypocalcemia is the reversibility of these manifestations in virtually every case including correction of prolonged QT interval (QTc) and restoration of LVEF.[23] Congenital conditions, such as DiGeorge syndrome (a part of the CATCH 22 spectrum of disorders) are associated with conotruncal anomalies of the heart as well as thymic hypoplasia and hypoparathyroidism.[24] Kearns-Sayre syndrome, a mitochondrial myopathy that presents with cardiac conduction abnormalities, pigmentary retinopathy, and progressive external ophthalmoplegia may be associated with endocrine dysfunction such as hypoparathyroidism, diabetes and short stature.[25]

The Pituitary Gland

Prolactin

Lactotroph cells of the anterior pituitary synthesize and secrete prolactin under the inhibitory control of hypothalamic factor dopamine. Certain studies have demonstrated an association of high prolactin with insulin resistance, dyslipidemia, hypertension, cardiovascular, and all-cause mortality over a 10 year follow-up period.[26-28] Peripartum cardiomyopathy (PPCM) has been speculated to be mediated by a 16 kDa prolactin fragment. Prolactin inhibition with dopamine agonists (DAs) such as bromocriptine is being explored as a novel PPCM treatment in addition to the implementation of standard heart failure regimens.[29]

DAs such as bromocriptine, cabergoline, and quinagolide that are used in the management of prolactinomas have been linked to the development of regurgitant valvular lesions such as tricuspid, mitral and aortic regurgitation if used for a long duration.[30] An ergot-derived DA pergolide has been shown to induce fibrotic changes in valve leaflets and the mitral subvalvular apparatus, causing thickening, retraction, and stiffening of valves resulting in valve regurgitation.[31] Till date, there is no conclusive evidence of a definite association between DA use in the management of hyperprolactinemia and valvulopathies.[32]

Growth hormone

Both growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are important mediators of cardiac development which are vital for the regulation of the cardiovascular system.[33] GH deficiency (GHD) or excess may result in adverse cardiovascular outcomes.

Growth hormone deficiency

GHD syndrome is a well-defined constellation of symptoms and signs identified in adults with GHD characterized by an impairment of cardiac mass and performance with visceral obesity, insulin resistance, low high-density lipoprotein (HDL) cholesterol, vascular atherosclerosis with endothelial dysfunction, and hypercoagulability, all of which are associated with an increased cardiovascular risk.[34] Cardiac morphology at echocardiography associated with GHD is characterized by a reduced cardiac mass, notably a decreased LV mass index and LV diameter with a decrease of LV walls, and interventricular septum thickness. Although these findings have been confirmed in childhood-onset GHD, they are not consistently described in adult-onset GHD patients.[35,36] A systolic dysfunction both at rest and after exercise with decreased exercise tolerance has been reported in young patients with GHD.[37] Carotid arterial IMT, an indicator of early atherosclerosis, is also increased in GHD.[38]

Both elevated BP and decreased systolic BP have been reported in subjects with GHD. Differences in age group, duration of GHD, and genetic heterogeneity may explain these contradictory findings.[39,40] Dyslipidemia seen in GHD is characterized by an increase in serum triglycerides, total cholesterol, and LDL-cholesterol with decreased HDL-cholesterol levels.[41]

Some metabolic disturbances secondary to GHD such as low HDL and elevated LDL may be partially or fully reversed following growth hormone replacement therapy (GHRT). Improvement in cardiac output, LV mass, stroke volume, central obesity, endothelial dysfunction (by mediating NO production through IGF-1), and arterial stiffness usually occur with GHRT.[42-45] After an initial transient worsening, GHRT improves insulin sensitivity by increasing IGF-I levels and reducing fat body mass and visceral adiposity.[42,46]

Acromegaly

Acromegaly, a state of GH excess significantly impacts the cardiovascular system with multiple manifestations as shown in Table 1.[46-48] Hypertension may be seen in 20%–50% of patients with acromegaly.[49] Acromegalic cardiomyopathy is divided into early, intermediate, and late stages. Progression to the late stage is characterized by systolic and diastolic dysfunction, myocardial hypertrophy, and ventricular dilatation with increased peripheral vascular resistance. Progression to heart failure is seen in up to 3%–10%.[48] The use of somatostatin analogs for successful disease control may enhance cardiac function by decreasing volume overload, improving diastolic function, and promoting reduction in wedge and pulmonary pressures. However, valvular dysfunction may persist despite correction of hormonal levels.[50] Somatostatin analogs show benefit in reducing arrhythmogenicity in patients with acromegaly. Cardiovascular disease secondary to atherosclerosis in GH excess states is associated with increased mortality which persists even after treatment.[50]

Table 1: The cardiovascular manifestations of acromegaly

Structural abnormalities	
Structure involved	**Manifestation**
Myocardium	Myocardial hypertrophy
	Ventricular dilatation
	Interstitial fibrosis and inflammation
Valvular lesions	
(Due to myxomatous valve disease secondary to abnormal extracellular matrix regulation)	Aortic insufficiency
	Mitral insufficiency
Vasculature	Increased arterial stiffness
	Hypertrophy and fibrosis of tunica of arterial wall
	Atherosclerosis
	Endothelial dysfunction
	Coronary artery disease
	Increased peripheral resistance
	Increased arterial stiffness
ECG changes and ECHO findings	
Prolonged QT intervals	
Left axis deviation	
ST-T wave depression	
Late potentials	
Septal Q-waves	
LVH	
Ventricular dilatation on ECHO	
Mitral valve regurgitation	
Systolic and diastolic dysfunction on ECHO	
Decreased early to late mitral velocity	
Conduction abnormalities	
Atrial fibrillation	
Atrial ectopic beats	
Ventricular ectopics	
Ventricular tachycardia	
Supraventricular tachycardia	
Sick sinus syndrome	
Bundle branch blocks	

ECG: Electrocardiogram, ECHO: Echocardiography, LVH: Left ventricular hypertrophy

Adrenocorticotropic hormone

The chief role of adrenocorticotropic hormone (ACTH) is regulation of adrenal cortisol secretion. A pathological elevation of ACTH is observed in endogenous causes of excessive secretion from a pituitary or extra-pituitary (ectopic) source. The end-point of elevated ACTH is a state of hypercortisolemia or Cushing's syndrome (CS).

Cushing's Syndrome

Hypercortisolism is associated with hypertension, central obesity, insulin resistance, dyslipidemia with changes in clotting and platelet function. Hypertension is present in about 80% and diabetes/impaired glucose tolerance is seen in more than 50% of adult patients with endogenous CS which may occur due to several causes. In addition, endothelial dysfunction, hyperlipidemia and a state of hypercoagulability predispose them to increased risk of cardiovascular events such as myocardial infarction and strokes. The mechanisms of hypertension in CS are many and are as shown in Table 2.[51]

Hypertension improves with treatment of CS though the probability of resolution declines with long-standing hypercortisolism. Other metabolic derangements such as impaired fasting glucose and glucose tolerance and diabetes mellitus secondary to increased insulin resistance may adversely impact the cardiovascular system by promoting atherosclerosis.[52,53] Cardiac structural and functional abnormalities include LVH, diastolic and systolic dysfunction which may be reversed following correction of hypercortisolism.[54]

Adrenal Glands

Cortisol and aldosterone from the adrenal cortex and catecholamines from the medulla exert significant effects on the cardiovascular system. Hormonal excess or deficiency may alter cardiac function significantly.

Aldosterone

Aldosterone excess secondary to either genetic causes or primary aldosteronism (PA) (hyperplasia or aldosterone-secreting adenomas) is known to cause hypertension resulting in cardiac changes such as LVH and cardiac fibrosis. The direct action of aldosterone on myocardium, independent of pathological changes induced by the development of hypertension including up-regulation of the synthesis of collagen I and III, pro-inflammatory mediators, reactive oxygen species and activation of angiotensin II production, results in increased LV mass, myocardial fibrosis, and perivascular inflammation. The increase in LV mass has been found to be out of proportion to the degree of volume or pressure overload. Patients diagnosed with PA have a greater LV end-diastolic diameter as compared to those with essential hypertension, with no significant difference in the end-systolic diameter. The increased LV diastolic dimension may be attributed to cardiac volume overload due to the renal effects of aldosterone such as sodium retention and also due to direct inotropic effects.[55] These features are known to regress following treatment for excess aldosterone.[56]

Adrenal deficiency

It is a state of glucocorticoid deficiency which is mostly associated with a mineralocorticoid deficiency as well. ECG abnormalities seen in this condition are prolonged QT intervals, low voltage, prolonged PR or QRS interval, inverted T waves, and depressed ST segment. Steroids are needed for the maintenance of membrane calcium transport in the cardiac SR.[57] A decline in microsomal phosphorylase activity has been noted in rat heart muscle following adrenalectomy leading to reduced glycogenesis and cardiac contractility.[58]

Pheochromocytoma

Pheochromocytoma is a neuroendocrine tumor of enterochromaffin cells of the adrenal medulla (85%–90%)

Table 2: Mechanisms of hypertension in Cushing's syndrome

Pathogenesis	Mechanisms of hypertension
Increased plasma volume	11β HSD2 inhibition
	Redistribution of sodium to extracellular spaces
	Co-secretion of mineralocorticoid hormones deoxycorticosterone, corticosterone)
	Greater cardiac output mediated by epinephrine-induced in turn by the increased PNMT activity
	Activation of ouabain-sensitive Na-K dependent ATPase
Increased peripheral resistance	Increased circulating levels of angiotensin II due to the increase of hepatic angiotensinogen synthesis (levels about twice as high in patients with CS)
	Increased vascular reactivity to vasoconstricting stimuli of angiotensin II, catecholamines, vasopressin, erythropoietin, etc.
	Inhibition of vasodilatory systems such as nitric oxide, kinin/Kallikrein, prostacyclin
	Inhibition of peripheral catabolism of catecholamine, in particular of norepinephrine
	Direct action of glucocorticoids on cardiovascular receptors
	Increased calcium uptake and calcium channel antagonist binding in vascular smooth muscle cells
	Decreased ANP-mediated cyclic guanosine monophosphate formation (leading to diminished vasodilatation by ANP)
	Genetic factors also intervene as suggested by the identification of some glucocorticoid receptor polymorphisms which are associated with a greater receptor sensitivity

PNMT: Phenylethanolamine-N-methyltransferase, CS: Cushing's syndrome, ANP: Atrial natriuretic peptide, HSD2: Hydroxysteroid dehydrogenase 2

or extra-adrenal sympathetic paraganglia. It may manifest as paroxysmal or sustained hypertension in over 80%–90% of patients.[59] Hypertension secondary to a pheochromocytoma may result in exaggerated variability with an increased incidence of target organ damage. Secondary hypertension is characterized by increased peripheral resistance with a reduced cardiac index.[59] Hypertension may be related to increased secretion of catecholamines from sympathetic nerves, possibly secondary to increased noradrenaline in sympathetic stores due to uptake from the circulation.[60] Patients with a pheochromocytoma exhibit orthostatic hypotension with a decreased stroke volume and impaired adaptation of total peripheral resistance which implies inadequate arteriolar and venous reflexes.[61] Severe hypotension may also occur in the postoperative period following resection of a pheochromocytoma.[62,63] Arrhythmias may be seen in around 20% of patients which include sinus tachycardia, supraventricular, and ventricular tachycardia and sick sinus syndrome. Pathological myocardial changes may result in cardiomyopathy, ischemic heart disease, cardiogenic shock, or myocardial stunning. Around a quarter of patients suffering from a pheochromocytoma may have an underlying dilated or hypertrophic cardiomyopathy.

ECG changes may include inverted T waves, QT prolongation, poor R-wave progression, and right axis deviation. Echocardiographic features of cardiomyopathy include a dilated LV with decreased contractility and ejection fraction, dilated left atrium with an elevated end diastolic pressure, and septal hypertrophy. Catecholamine-induced cardiomyopathy usually improves after surgical resection of a pheochromocytoma, but complete resolution depends on early detection and management.

Gonadal Disorders

Turner syndrome

Turner syndrome is reported to have a prevalence of 1 in 2500 live births, with complete or partial absence of one X-chromosome and is characterized by short stature, ovarian failure, and infertility. Congenital heart defects (CHD) are seen in about 30% of patients and include bicuspid aortic valves, coarctation and dissection of aorta, aortic valve dysplasia, mitral valve abnormalities including ballooning and parachute valves. Conduction and repolarization abnormalities have been reported, and QTc prolongation may occur. Hypertension is seen in about one fourth of patients. The congenital and acquired cardiac abnormalities in Turner syndrome tend to progress warranting early, aggressive, and continued screening and treatment to reduce associated morbidity.[64]

Noonan syndrome

Noonan syndrome is characterized by dysmorphic facial features, CHD, short stature, webbed neck, chest deformities, and undescended testes in males. Cardiac malformations include pulmonary stenosis, with or without pulmonary valve dysplasia and hypertrophic cardiomyopathy. Other reported anomalies include atrial septal defects, atrioventricular septal defects, left-sided obstructive lesions, tetralogy of Fallot, and patent ductus arteriosus. The mechanism of occurrence of cardiac defects has been attributed to formation of abnormal cardiac jelly and extracellular matrix.[65]

Conclusion

Endocrine dysfunction has an adverse impact on the cardiovascular system which may be either due to an endocrine abnormality or an adverse reaction to drugs used in the management of these conditions. Most cardiovascular changes are reversible if detected early and the underlying endocrinopathy is corrected.

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Conflicts of interest

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