Cardiovascular Endocrinology

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Shared Pathways and Clinical Crossroads

Edited by

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Preface

CARDIOVASCULAR ENDOCRINOLOGY

In the last two to three decades, cardiovascular disease and diabetes have emerged as a major public health problem. This is partly related to the epidemic of obesity, which plays a major role in the pathogenesis of both diabetes and cardiovascular disease. In addition, several other hormones and cytokines have been shown to play an important role in the regulation of the vascular system. This increase in the clinical problems of cardiovascular disease in a large segment of the population has brought together the two disciplines of vascular biology and endocrinology. This book highlights the many common pathophysiological processes involved in this epidemic and the common clinical manifestations that result from them.

The book has several important contributions from distinguished workers in the field. Derek Leroith begins with a novel view of the hormonal regulation of the vascular system, starting, not surprisingly, with pituitary and hypothalamic factors that may impact vascular disease.

The problems of diabetes and cardiovascular disease are extensively covered in a number of chapters, including a review of the epidemiology of the problem by James Meigs, and the important disruption of the nitric oxide signaling system, as well as the role of fatty acids and cytokines in the development of this problem, which are discussed by Bobby Nossaman and Gunther Boden, respectively.

Management of the problem of cardiovascular disease and diabetes in relation to screening of patients using modern cardiovascular techniques is discussed by Paolo Raggi, followed by discussions of the role of insulin (Dandona) and insulin sensitizers (Thethi), and their potential for impacting cardiovascular health.

Endocrine hypertension has long been recognized as an important contributed to cardiovascular morbidity, and the renin-angiotensin system plays a key role in not only endocrine-mediated hypertension, but hypertension in general. This system and its impact on cardiovascular events is discussed by Jim Sowers and followed by a discussion on microalbuminuria and chronic kidney disease by George Bakris.

Adiponectin has emerged as a natural endogenous vascular protective and anti-inflammatory substance of considerable importance in the context of cardiovascular endocrinology, and is reviewed by Mandeep Bajaj. Another important peptide hormone that affects vascular function is the group of natriuretic peptides, reviewed by Kailash Pandey.

Finally, the interaction of sexual dysfunction and cardiovascular disease has attracted much attention, and the overlap of these conditions and therapeutic approaches to overcome them are reviewed by Glen Matfin. Closely related is the effect of testosterone, often neglected as a player in vascular function and reviewed by Alan Seftel.

This textbook of cardiovascular endocrinology comes back full circle to the role of insulin-like growth factors and cardiovascular disease with the final contribution by Patrice Delafontaine.

Finally, I would like to dedicate this book to our many patients who have participated in clinical research to improve our understanding of their disease process. More importantly I wish to dedicate it to the people of New Orleans and wish that city a speedy recovery.

Contents

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Color Plates

Color Plate 1 Kaplan-Meier estimates of the probability (with 95% confidence intervals) of death from coronary heart disease in 1059 subjects with type 2 diabetes and 1378 nondiabetic subjects with and without prior myocardial infarction (MI) in a Finnish population-based study (Chapter 2, Fig. 1; *see* discussion on p. 21).

Color Plate 2 Example of myocardial perfusion performed by echocardiography after intravascular injection of echocontrast (microbubbles). The arrows point at an area of decreased perfusion of the inferior wall of the myocardium during dobutamine stress (panels B and C) (courtesy of Dr. Sanjiv Kaul, Oregon Health and Science University, Portland, OR) (Chapter 7, Fig. 3; *see* discussion on p. 101).

Color Plate 3 Examples of nuclear myocardial perfusion imaging of the left ventricular myocardium. Patient A shows a homogeneous distribution of the radioactive tracer both at rest and during stress. Patient B shows a moderate size defect in the anterior wall of the left ventricle (yellow arrows) during stress (top row images). The defect has disappeared (i.e., is reversible) during rest (bottom row images). Patient C demonstrates a large and fixed perfusion defect of the inferolateral wall (white arrow heads) and a partially reversible defect of the apex of the left ventricle (green arrows) (Chapter 7, Fig. 4; *see* discussion on p. 102).

Color Plate 4 An example of assessment of left ventricular function on PET imaging. The calculated left ventricular ejection fraction is 74%. The top row shows diastolic images of the left ventricle (the chamber is larger and the walls are thinner) while the bottom row shows systolic frames (the chamber is almost virtual and the walls are thick) (Chapter 7, Fig. 5; *see* discussion on p. 102).

Color Plate 5 Guidelines proposed by the American Diabetic Association on performance of exercise stress testing, with or without an imaging modality associated with it, in diabetic patients (modified from reference *(54)*) (Chapter 7, Fig. 10; *see* discussion on p. 112).

Color Plate 6 New standard of care from the American Diabetic Association on performance of exercise stress testing, with or without an imaging modality associated with it, in asymptomatic diabetic patients (modified from reference *(102)*) (Chapter 7, Fig. 11; *see* discussion on p. 112).

1 Hormonal Regulation of the Vascular System: An Overview

Ronald Tamler, MD, PhD,
and Derek LeRoith, MD, PhD

CONTENTS

SUMMARY

This chapter discusses hormonal influence on the vasculature. Catecholamines are the best-known and classic stimulators of vascular tone. The rennin–angiotensin–aldosterone system (RAAS) induces vasoconstriction and may damage the vasculature. Sex steroids have gender-dependent disparate genomic and rapid, nongenomic effects on the vasculature. Insulin may have beneficial properties, whereas growth hormone and IGF-1 imbalances are tied to coronary heart disease (CHD). Adipokines are produced in the fat tissue and also affect the vasculature in many ways. While this overview can only briefly touch on all the systems mentioned, later chapters provide greater depth to the reader.

Key Words: Insulin resistance, Hypertension, Coronary heart disease, Angiotensin, Estrogen, Testosterone

INTRODUCTION

When Thomas Addison discovered that the adrenal glands were essential for life *(1)* and later George Oliver and Edward Sharpey-Schafer purified adrenaline in the nineteenth century *(2)*, they were the first to discover the importance of hormonal control of the vasculature. In the

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twenty-first century, we are aware of a greater number of hormonal and nonhormonal vascular stimuli with highly complex interactions. Still, there is a sense that many pathways need to be better understood and many discoveries yet to be made.

Arterial blood pressure is influenced by vascular tone and cardiac output, both of which are subject to hormonal control. In addition to an inner coating with endothelium, arteries – particularly the resistance vessels, called arterioles – sport a surrounding muscular layer in the tunica media. This layer, directly and indirectly regulated by parasympathetic and hormonal influences, is responsible for arterial tone, a significant contributor to diastolic blood pressure. Meanwhile, the endothelium is influenced by a powerful vasorelaxant, endothelial-derived relaxing factor (EDRF), now identified as nitric oxide (NO) *(3)*, which in turn counteracts the vasoconstrictive effects of catecholamines and angiotensin II (ATII) *(4)*. Beyond acute vasoconstriction, chronic alterations of the vasculature, such as atherosclerosis are also hormonally influenced and can increase systemic blood pressure. Finally, cardiac output, the product of stroke volume and heart rate, affects systolic blood pressure and is regulated by parasympathetic and hormonal activity.

Hormones therefore influence the vasculature in multiple ways: by regulating volume status, modifying smooth muscle contractility directly and through the NO pathway, and, finally, by altering cardiac output.

In this chapter, we can only attempt to give a brief overview on what is known about how hormones control the cardiovascular system. We will address only a limited number of hormonal pathways as examples of the interaction between the endocrine and cardiovascular systems. The following chapters will provide a deeper and more thorough understanding of individual pathways.

1. Catecholamines

Catecholamines are a family of hormonally active amines derived from the amino acid tyrosine. Adrenaline (also called epinephrine) and dopamine can act centrally as neurotransmitters, whereas norepinephrine fulfills that role in the periphery. When found in the bloodstream, these compounds are typically spillover from neuronal ganglia *(5)* or synthesized in the adrenal medulla in response to sympathetic activation, the "fight or flight" reaction. General effects include increased heart rate, blood pressure, and stroke volume, but vascular catecholamine effects can vary and depend entirely on G-protein-coupled membrane receptors:

α1-Adrenoreceptors are divided into three subtypes (α1A, α1B, and α1D) with different efficiencies of activating phospholipase C via G-protein. Subsequently, the second messengers inositol triphosphate and diacylglycerol are increased and ultimately lead to calcium influx into the cell. The result is contraction of smooth muscle, leading to higher resistance and higher arterial blood pressure. α1-Adrenoreceptors are mainly stimulated by norepinephrine, but can also be activated by adrenaline.

α2-Receptors are also classified into three subtypes. They are coupled with a GTP-binding protein that inhibits adenylyl cyclase, eventually preventing the opening of Ca and K channels. α2 receptors are observed in noradrenergic neurons. While α1 receptors are typically found near sympathetic nerve terminals, α2 receptors are found extrajunctionally and are probably activated mainly by circulating catecholamines.

β-Adrenoreceptors are coupled to a stimulatory G-protein, leading to increased cAMP levels and calcium influx. They are also divided into three subtypes:

Cardiac β1 receptors counter vagal effects and they mediate positive inotropic, chronotropic, and dromotropic effects of catecholamines, mainly noradrenaline derived from sympathetic nerve activity. Over longer periods of time, these receptors, together with aldosterone from the

renin-angiotensin-aldosterone system (RAAS), mediate cardiotoxicity. Selective inhibition of β1 receptors has proven an effective treatment *(6)*, but even greater survival benefit is seen with additional blockade of the RAAS *(7)*.

β2-Receptors mediate vasorelaxation and are stimulated by circulating epinephrine, but not by norepinephrine. Due to the selective response, a counterintuitive drop in blood pressure can sometimes be observed when adrenaline is administered and norepinephrine-sensitive α1 receptors are blocked. Depending on distribution and concentration of adrenoreceptors in the vasculature, vasodilation may outweigh vasoconstrictive effects. β2 receptors are found on the endothelium and are thought to mediate their vasodilatory effects through the NO pathway: removal of endothelium and pretreatment with L-NAME may both curb vasorelaxation *(8)*. β2-adrenoreceptor stimulation activates via increased cAMP levels cleaving of L-arginine and NO production, which in turn leads to cGMP formation and vasodilation.

β3 receptors also mediate vasodilation and are not blocked by propranolol or other β-blockers routinely used in practice *(9)*. However, a more fascinating function may lie in their mediation of lipolysis in visceral fat *(9)*, which in turn plays a role in obesity and the metabolic syndrome. Metabolically active adipose tissue enhances atherogenesis via inflammatory cytokines such as interleukin-6 (IL-6) or tumor necrosis factor-alpha (TNF-a) and directly regulates vasoconstriction via angiotensinogen *(10)*.

Dopamine can occupy alpha- and beta-adrenergic receptors when given in higher, pharmacologic concentrations, but mainly acts through five subclasses of D receptors. In the kidney, dopamine acts as an ATII antagonist by enhancing natriuresis via tubular D1-receptors and directly decreasing ATII production. The net effect is lower systemic blood pressure *(11)*.

2. Renin-angiotensin-aldosterone system (RAAS)

The glycoprotein renin is produced in the juxtaglomerular apparatus of the afferent renal arterioles in response to hyponatremia and hypotension. Renin cleaves angiotensinogen, which is mainly produced in the liver and is elevated in patients with visceral adiposity and the metabolic syndrome in general. The resulting biologically inactive ATI is converted to the vasoconstrictive ATII by angiotensin-converting enzyme (ACE) in the pulmonary vasculature. ACE-mediated vasoconstriction is potentiated by degradation of bradykinin, a vasodilatory agent. Cardiovascular effects of ATII throughout the body are mediated by the transmembranous AT1 receptor, which is coupled to a G-protein. Activation results in decreased cAMP levels with subsequent Ca influx and vasoconstriction and increased protein kinase C levels. The latter is a pathway shared with other hormonal regulators, such as insulin. In addition to systemic effects, there are several organ systems in which mRNA for all components of the RAAS can be found and thus operate independently: renal autocrine and paracrine activity of the RAAS in general and ATII in particular has been described for vasoconstriction of the afferent arterioles with subsequent reduction in renal blood flow *(12)*. It is also held responsible for enhanced tubular Na/H exchange and Na/K ATPase activity *(13)*, leading to sodium reabsorption, and modified tubuloglomerular feedback sensitivity *(14)*.

Similar to the kidney, the myocardium features receptors for renin, angiotensinogen, and ATII *(15)* in fibroblasts and myocytes, as do the endothelium and smooth muscle of the coronaries. In fact, most ATII acting on cardiac tissue is not derived from the circulation, but is rather the product of the local cardiac RAAS *(16)* and conversion by chymase *(17)*. Renin, glucocorticoids, estradiol, thyroid hormone, and atrial natriuretic peptide all increase local production of angiotensinogen *(18,19)*, and mechanical stretch of the myocardium leads to increased local ATII levels *(20)*. ATII can stimulate local production of angiotensinogen in the kidney and the heart, thus inducing positive feedback *(21)*.

ATII induces vasoconstriction via increased free radical production *(22)*, by modulating the endothelial NO pathway *(23)* and directly through its own AT1 receptor. However, its best-known endocrine effect is stimulation of aldosterone production in the adrenal gland. Interestingly, while aldosterone production is activated by systemic ATII, local RAAS effects from the zona glomerulosa *(24)* have also been described.

Aldosterone has long-known effects on sodium retention and hypertension *(25)*. Other effects are cardiac hypertrophy and vascular fibrosis *(26)*. It probably exhibits a contradictory effect in that it facilitates endothelial-dependent vasodilation and vascular smooth muscle cell (VSMC)-mediated vasoconstriction *(27)*. Nongenomic, rapid effects of aldosterone include dose-dependent myosin light-chain phosphorylation, which can be inhibited by spironolactone, and phosphatidylinositol 3-kinase (PI3k) inhibition in VSMCs. The result is a contraction, which apparently can also be generated by estradiol and hydrocortisone *(28)*. Aldosterone antagonists, such as eplerenone or spironolactone, have been shown to improve clinical outcomes in patients with heart disease *(29)* and exert protective effects on the endothelium *(30)*.

3. Glucocorticoids

Glucocorticoids may exert vascular effects by cross-stimulation of pathways used by other steroid hormones, such as aldosterone *(31)*. Produced in the adrenal cortex or administered as drugs, they exert nuclear effects by binding to a ubiquitous ligand-activated transcription factor *(32)*. Anti-inflammatory properties *(33)* and increased insulin resistance are well described. In animal models, highly dosed glucocorticoids nongenomically activate endothelial nitric oxide (eNOS) and thus improve endothelial function *(34)*. However, the opposite effect has been described as well, and generation of reactive oxidant species has been invoked as the provoking mechanism responsible for decreased endothelial reactivity *(35)*. While the exact mechanism of action on the vasculature demands further attention, it should be noted that patients with Cushing's disease, a state of chronic glucocorticoid excess, have increased carotid intima-media thickness *(36)* and a higher risk of cardiovascular disease *(37)* that may persist even beyond cure *(38)*.

4. Insulin

Insulin resistance is commonly seen in both obesity and type 2 diabetes, a condition associated with increased cardiovascular risk *(39)*. While many other factors such as hyperglycemia, hypertriglyceridemia, and inflammatory cytokines affect the vasculature, insulin itself has direct effects. Acting via the insulin receptor signaling pathways, particularly the PI3kinase/Akt pathways, insulin induces eNOS activity in endothelial cells, leading to increased NO production *(40)*. This in turn affects the vascular smooth cells and leads to vasodilation. On the other hand, insulin stimulates production of endothelin-1, PAI-1, as well as the adhesion molecules VCAM-1 and E-selectin in endothelial cells via the ERK pathway. Insulin is thus capable of inducing vasodilation in a NO-dependent manner, increasing blood flow to skeletal muscle, for example, which in turn increases glucose uptake in skeletal muscle *(41)*.

Insulin, in addition, can attenuate the contractility of VSMCs by opposing increases in cytosolic calcium through the voltage-dependent sensitive calcium channels. These effects are apparently also mediated by NO.

Under certain circumstances of insulin resistance, endothelial dysfunction can be explained by the altered state of the insulin-stimulated PI3k/Akt pathway. As in the case of skeletal muscle, hyperglycemia, hyperlipidemia, increased oxidative stress, and increased inflammatory cytokines inhibit the PI3k/Akt pathway. In contrast, the mitogen-activated protein

kinase (MAPK) pathway is unaffected and the insulin signaling leads to excessive production of vasoconstrictor molecules such as endothelin-1, leading to deleterious effects on the vasculature *(40)*.

Insulin also has effects on the blood pressure, which may affect cardiovascular outcomes. Insulin enhances renal sodium retention at the distal tubule, thereby expanding the intravascular compartment. Its effects on the MAPK pathway in the VSMC in insulin-resistant patients may include VSMC proliferation. Finally, it may affect the sympathetic nervous system causing vasoconstriction under conditions of insulin resistance *(42,43)*. The final outcome is an increase in blood pressure in patients who are obese or have type 2 diabetes.

Thus, insulin under physiological conditions is generally a positive mediator of vascular function, while insulin resistance and the concomitant hyperinsulinemia may be deleterious and causative in cardiovascular disease.

5. GH and IGF-1

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) also have seemingly paradoxical effects on the cardiovascular system. Acromegalics demonstrate two significant cardiovascular abnormalities: hypertension and cardiomyopathy. Impaired endothelium-dependent vasodilation may be secondary to exaggerated sympathetic tone with enhanced vasoconstriction. Furthermore, increased Intima-media thickness (IMT) in the carotid arteries has been demonstrated in cases of acromegaly. Whether these changes are due to the increased GH/IGF-1 levels or secondary to the insulin resistance in these patients is still undefined. While circulating IGF-1 is primarily expressed in the liver, it is also produced in VSMCs, platelets, circulating macrophages and all other tissues of the body *(44)*. Thus there is an apparent endocrine and paracrine/autocrine effect of IGF-1 on the cardiovascular system.

IGFs have been demonstrated to increase proliferation of VSMCs and vascular endothelial cells *(45–47)*. Furthermore, IGFs stimulate monocyte migration into the arterial wall, as well as the uptake of modified low-density lipoprotein (LDL) particles and the release by macrophages of proinflammatory cytokines; all of which can add to the macrovascular changes *(48,49)*.

Interestingly, GH deficiency in children results in smaller hearts, which is reversible with GH replacement therapy *(50)*. Similarly in adult-onset GH deficiency, GH replacement reverses the defect *(51)*.

GH replacement also has a significant effect on improving the lipid profile Apo B-100 and LDL cholesterol decrease *(52)*. Arterial distensibility improves probably due to GH's effect on endothelial-derived NO, and plaque formation improves as shown by changes in IMT. This is associated with reductions in proinflammatory cytokine production *(52)*. Since the short-term use of GH makes insulin resistance worse, and long-term use is associated with reduced Insulin resistance (IR), the positive cardiovascular effects require continued replacement.

Additional effects have been demonstrated on the heart. Combined deletion of insulin receptor and the IGF-1 receptor genes in skeletal and cardiac muscle resulted in a significant reduction in size of the cardiomyocyte. Specific overexpression of IGF-1 induced increase in cardiomyocyte size and function. Thus IGF-1 (and perhaps insulin) may be important for cardiac development *(53)*.

Thus a paradox exists in that acromegaly with elevated GH/IGF-1 levels is associated with endothelial changes and cardiomyopathy that is at least partially reversible or prevented by therapeutic restoration of normal GH/IGF-1 levels *(54)*. On the other hand hypopituitarism and low IGF-1 cause underdevelopment of the cardiac muscle.

Furthermore, both acromegalic and GH-deficient individuals are at increased risk for myocardial infarction *(55)*. Some studies have suggested an antiatherogenic and cardioprotective effect of IGF-1 *(56)*, while others have shown higher circulating IGF-1 levels associated with Coronary heart disease (CHD) *(57)*. At the cellular level IGF-1 stimulates VSMC and endothelial cell proliferation *(45)*, migration of monocytes into the arterial wall, and uptake of modified LDL and release of proinflammatory cytokines by macrophages *(48)*. On the other hand IGF-1 acts as a survival factor for VSMCs which prevent plaque instability and rupture *(58)*.

Overall the consensus of many studies is that there is a relationship between IGF-1 levels and CHD, and the deleterious effects are related to both excess and deficiencies in IGF-1 levels *(59)*.

6. Sex steroids

The effect of sex steroids on the vasculature is a very active target of discussions and ongoing investigations. The risk of CHD in premenopausal women is much lower than in men and only after the menopausal estrogen decline does it adjust to the risk seen in men *(60)*. This observation shaped the opinion that estrogen must have beneficial effects on the vasculature, whereas testosterone was thought to have deleterious effects *(61)*. Subsequent large clinical trials with postmenopausal estrogen replacement therapy and hormone replacement therapy in women, however, yielded disappointing results *(62–65)*. The current view is more differentiated and gender-specific *(66)*. Sex hormones induce conformational change in their receptors and often require a cell-specific coregulator to exert an extranuclear effect or specific gene expression *(67)*. Different ligands may induce different conformational changes with different targets in the same receptor, which explains the differences in action seen in various selective estrogen receptor modulators (SERMs) *(68)*. In addition to direct effects on the vasculature, sex steroids exert indirect effects via the adipose tissue and lipoprotein metabolism, regulation of the actions of other hormones (such as insulin), and modulation of inflammation, all of which influence the vasculature *(69,70)*.

ESTROGEN

There are three estrogens of relevance: the prevalent but mildly active estrone, the more potent estradiol, and finally estriol, which is a product of the placenta. Most research centers on effects of estradiol. There are two known estrogen receptors (ERs), the classic ER-α and the more recently discovered ER-β *(71)*, which differ significantly from each other in their ligand-binding domains and their distribution throughout the body *(72,73)*. Both are present in endothelial cells, but ER-β receptors are uniquely expressed in VSMCs *(74)*. Different SERMs may induce disparate effects by binding more strongly to one receptor than the other *(68)*.

The classic estrogen response involves receptors that are essentially ligand-activated transcription factors and regulate gene expression with results lasting hours or even days. Targets include E-selectin and VCAM-1 modulation, which in turn affect cell adhesion and increase expression of COX-1 and PGI2, leading to increased inflammation *(75,76)*. IL-6 increases expression of ER-β and the androgen receptor (AR) in the smooth muscle cell. Conversely, IL-6 is increased by estrogen *(76)*. Estrogen also increases expression of progesterone receptor on endothelial cells. Another important area is that of vascular remodeling and angiogenesis: Estrogen supplementation in the immediate aftermath of vascular injury promotes vascular regeneration, which relates to increased expression of collagen, elastin, and matrix metalloproteinase. On the other hand, estrogen has a direct inhibitory effect on vascular smooth muscle growth and neointima formation. Increased expression of nitric oxide synthase (NOS),

MAPK, and PI3 also leads to a higher availability of response elements for swifter vasodilatory mechanisms *(75)*.

Estrogens lead to rapid vasodilation by nongenomic pathways in men and women alike: membrane ERs, which are a product of the same transcript as the classic nuclear receptors, indirectly activate the MAPK and PI3k/Akt pathways within minutes *(77)*. Results of this nongenomic estrogen action are increased NO derived from eNOS and inducible NOS (iNOS) as well as endothelial rounding, a factor that makes it more difficult for leukocytes to adhere and promote atherogenesis.

Indirect vascular effects generated by estrogen include a favorable lipoprotein profile with decreased LDL and lipoprotein(a) levels as well as increased HDL levels, and modulation of hemostasis/fibrinolysis with decreased expression of PAI-1, tPA, and prothrombotic proteins *(76)*.

PROGESTERONE

The female gonadal steroid progesterone (Pg) mainly acts on classic reproductive tissues such as the placenta. A multitude of synthetic progesterones with varying degrees of androgenetic activity is in clinical use, mainly for contraceptive purposes. Although the Pg receptor is widely distributed throughout the vasculature *(78)*, little is known about its physiologic role. Vasorelaxant properties have been proposed after animal and in vitro data showed increased endothelial NOS activity *(77)*. In addition, enhancement of cyclooxygenase production and inhibited platelet aggregation have been demonstrated *(79)*. Similar to E2, Pg probably has rapid nongenomic effects, which by way of PI3k and protein kinase C generate a fast response in NO generation and on platelet function *(80)*.

Large clinical trials using HRT in postmenopausal women with E2 and Pg however found increased cardiovascular and cerebrovascular events *(64)*. Further investigation is required to reconcile the gap between the favorable physiologic data and poor outcomes in clinic trials. A prospective cohort study from the Framingham Heart Study that examined circulating estradiol in men found that those men with the highest estradiol levels had lower risk for cardiovascular events *(81)*. Men with defective mutations of estrogen synthesis or ERs have premature atherosclerosis which may be consistent with the view that estrogens yield some cardioprotective effect in men *(82,83)*. Indeed, the most recent prospective cohort study suggests higher endogenous estrogen levels are a better predictor of lower cardiovascular disease incidence than testosterone (T) or dehydroepiandrosterone sulfate (DHEAS) *(81)*.

ANDROGENS

DHEA and its sulfate (DHEAS) are produced in the adrenals and have mildly androgenic properties. Higher levels of DHEA and DHEAS correlate with lower incidence of cardiovascular disease. DHEA and DHEAS may serve as prohormones for downstream estrogenic hormones in men *(84–86)*. Of the many cohort studies investigating the correlation with cardiovascular disease *(81,87–91)*, one *(87)* suggested lower DHEAS levels in CHD survivors and two *(89,91)* delineated a trend toward benefit with higher DHEAS levels. However, a fairly recent prominently published study showed no benefit of DHEA supplementation in deficient men or women *(92)*.

The main androgen in humans is T, which is produced in the testicles and, to a lesser degree, in the ovaries and adrenals. T or the more potent dihydrotestosterone (DHT) interacts with the nuclear androgen receptor (AR) to cause changes in transcription. However, in vitro and in

vivo studies have found T to be a rapid coronary vasodilator *(93–95)* with intravenous administration of T improving endothelial function in men with CHD *(96)*. These rapid changes are not blocked by pretreatment with the AR blocker Flutamide and therefore must follow a rapid, nongenomic pathway. In addition, T may act as a calcium channel blocker in the VSMC *(97)*.

T levels decrease in men as they age, and hypogonadism is estimated to affect more than 20% of men over the age of 60; however, men with CHD are known to have lower T levels than age-matched controls with normal coronary angiograms *(98–100)*. So far, the numerous prospective studies examining the relationship between endogenous T and cardiovascular disease incidence in men *(81,101–107)* have not shown a clear association. Androgens at supraphysiologic doses have been associated with the development of left ventricular hypertrophy *(108)*, heart failure *(109)*, and dilated cardiomyopathy *(110)*. However, salutary effects have been reported with physiologic doses of transdermal T in men with heart failure *(111)*. Low T is associated with greater atherosclerotic burden, and replacement with T improves aortic atherosclerosis in animal studies. This observation is only partly explained by a lipid effect *(112–115)*. Although the burden of atherosclerosis may be reduced with elevated T, it may paradoxically result in increased cardiovascular events from decreased plaque stability. In vitro data show that, in macrophages derived from men, androgen treatment upregulates pro-atherogenic genes associated with lipoprotein processing, cell-surface adhesion, extracellular signaling, coagulation, and fibrinolysis *(116)*.

Higher T levels in polycystic ovary syndrome (PCOS) are correlated with the development of the metabolic syndrome and diabetes in premenopausal women, and the decrease in E:T ratio has often been faulted for the increase in postmenopausal CHD. However, endothelial function in postmenopausal women correlates positively with T levels, while T is felt to protect against carotid plaque burden *(117,118)*.

7. Other hormonal systems

Parathyroid hormone (PTH) is known to impact the cardiovascular system in a negative way. Patients with hyperparathyroidism exhibit higher mortality *(119,120)* due to higher incidence of hypertension *(121)* and cardiovascular disease *(122)* as well as other components of the metabolic syndrome, such as insulin resistance *(123,124)*. The common denominator is impaired endothelial function *(125)*, proliferation of VSMCs *(126)*, and calcium influx into the VSMC mediated by the PTH/PTH-rp-receptor. The result is increased vascular tone *(127)*. It should be noted that, while this factor has not yet found its way into the societal and NIH guidelines for parathyroidectomy *(128)*, many authors have been advocating for long-term cardiovascular risk to be included in the decision-making process for surgery *(129)*.

A recently published randomized controlled study in patients with subclinical hypothyroidism showed that L-T4 supplementation improved endothelial function *(130)*. The authors mainly invoked improved lipid profile for the beneficial cardiovascular profile. Meanwhile, the more active T3 was found to reduce peripheral vascular resistance by NO-dependent endothelial mechanisms as well as increased SMVC susceptibility to noradrenaline *(131)*.

Adipokines are bioactive mediators secreted by the adipose tissue that often go beyond the traditional role of cytokines. Proinflammatory markers such as TNF-a, IL-6, and IL-1 act as disruptors of the insulin signaling cascade and endothelial function. Leptin, a medium-sized peptide of 167 amino acids abundantly secreted by adipocytes, has a multitude of receptors throughout the body and is implicated in effects beyond its traditionally invoked role in the control of appetite. So far, we know that leptin inhibits growth of VSMC *(132)*. High leptin levels are associated with decreased arterial distensibility *(133)* and increased cardiovascular

mortality, particularly in patients with diabetes mellitus *(134,135)*. Resistin, which is 114 aminoacids long, is expressed by the bone marrow and peripheral mononuclear cells in humans, and controversy exists whether this peptide should be grouped with traditional adipokines *(136)*. It has been shown to promote inflammation *(137)* and proliferation of VSMC and endothelial cells *(138)*. Clinically, resistin appears to be linked to higher rates of cardiovascular disease in patients with diabetes *(139)*.

Adiponectin, which structurally belongs to the collagen family, is often described as the "good" adipokine: produced in the subcutaneous fat rather than visceral fat tissue, it is abundantly found in the bloodstream and is reduced in men, states of insulin resistance and cardiovascular disease *(140)*. Two receptors have so far been described, and although expression is ubiquitous, muscle and the liver are the main targets of adiponectin. They mediate activation of AMP kinase, PPARα, and, as a consequence, glucose uptake and fatty acid oxidation *(141)*. Thiazolidinediones (TZDs), which act as Peroxisome Proliferator-Activated Receptor (PPAR-γ) agonists, may unfold their beneficial effects on metabolism and endothelium alike by modulating expression of adiponectin and its receptors *(142)*.

CONCLUSION

As demonstrated in this brief overview, hormones influence the vasculature directly and indirectly. Catecholamines are the best-known and classic stimulators of vascular tone. The RAAS is an additional source of stimuli that may damage the vasculature. Sex steroids may show gender-dependent disparate genomic and rapid, nongenomic effects on the vasculature, and much research is needed to clarify the role of hormone supplementation. Insulin may have beneficial properties, whereas GH and IGF-1 are tied to CHD in both states of deficiency and excess. Finally, adipokines are a relatively novel group of agents that may directly, and through a variety of effects on hormonal axes and inflammatory pathways, regulate the vasculature. While this overview can only briefly touch on all the systems mentioned, later chapters provide greater depth to the reader.

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I Diabetes and Cardiovascular Disease