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Cardiovascular Endocrinology: A Game Changing Concept

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Abstract

Clearly, the term gets its wordy justification from two established medical disciplines (e.g. cardiology and endocrinology). Combining the two, however, contains more than just the mutual interest in, for instance, diabetes mellitus and its complications that, nowadays, are dominantly cardiovascular. Cardiovascular endocrinology must look beyond established hormonal axes for new ways of thinking, and this search should not be confined to identifying new markers of disease nor treatment strategies but help elucidate entirely new mechanisms that link the cardiovascular system with the plethora of blood-borne bioactive substances and their referred cellular targets.

Introduction

Clearly, the term gets its wordy justification from two established medical disciplines (e.g. cardiology and endocrinology). Combining the two, however, contains more than just the mutual interest in, for instance, diabetes mellitus and its complications that, nowadays, are dominantly cardiovascular. Cardiovascular endocrinology must look beyond established hormonal axes for new ways of thinking, and this search should not be confined to identifying new markers of disease nor treatment strategies but help elucidate entirely new mechanisms that link the cardiovascular system with the plethora of blood-borne bioactive substances and their referred cellular targets.

A second aspect of cardiovascular endocrinology involves the modern treatment of hypertension, cardiac arrhythmias, ischemic heart disease, and congestive heart failure by blocking or enhancing different hormonal systems. The clinical use of angiotensin-converting-enzyme inhibition or receptor blocking is now almost as commonly recommended as vitamin supplements and fish oils. Moreover, adrenergic receptor blockade constitutes a cornerstone in hypertension, cardiac arrhythmias and heart failure, and aldosterone inhibition is also an important supplement in heart failure treatment. Thus, when the heart does not fulfill its overall hemodynamic functions, neurohumoral activation takes over, usually with dire consequences for the suffering heart muscle. Clinicians must then intervene with treatment that lower morbidity and mortality using drugs targeted at endocrine axes. Thus, cardiovascular endocrinology has for a long time been applied in the modern medical treatment of cardiovascular patients, and the search for new enhancing or blocking 'endocrine' drugs is surely underway.

The central organ in the cardiovascular system is the heart itself. We review known heart-derived hormones, focusing on GDF15, myostatin, and ANP/BNP, and their biology in the cardiovascular system. GDF-15 is a divergent member of the transforming growth factor (TGF)-β family. In the

cardiovascular system, cardiac synthesis and secretion of GDF-15 are substantially increased in various cardiovascular diseases (e.g., heart failure)[1,2]. In addition to serving as a useful serum biomarker of cardiovascular disease, heart-secreted GDF-15 was recently shown to slow pediatric body growth by inhibiting liver growth hormone signaling, thus functioning as a heart-derived hormone[3]. Myostatin is another member of the TGF-β superfamily and was first discovered through screening in a mouse skeletal muscle library.5In the cardiovascular system, myostatin levels in both the heart and circulation are elevated in myocardial infarction or heart failure [4,5]. Clinical studies showed that plasma myostatin level was positively correlated with heart disease biomarker N-terminal pro-BNP in patients with congestive heart failure and with infarct size in acute myocardial infarction, which indicated that myostatin is a potential biomarker for these heart diseases. Cardiac myocytes produce and release natriuretic peptides with potent effects on renal sodium excretion, blood pressure and vascular permeability. Atrial and B-type natriuretic peptides are also plasma markers of heart disease, and measurement of the bioactive peptides, or their precursor fragments, is recommended in heart failure diagnostics. Unlike ANP and BNP, C-type natriuretic peptide (CNP) is widely expressed and not heart-specific[6,7]. However, cardiac synthesis of CNP is substantially elevated in patients with chronic heart failure[8]. Initially, the cardiomyocytes were believed to be fairly inefficient hormone-producing cells with little biosynthetic capacity. However, the heart cells are now known to be highly specialized endocrine cells with complex and elaborate post-translational processing. In perspective, it may therefore be worthwhile to look for other regulatory peptides produced in the heart, as endocrine cells often harbor more than one bioactive substance. One such substance has been suggested to be apelin, a small potent peptide with isotropic effects, which is otherwise produced in the stomach and the vasculature. The precise role for cardiovascular apelin clearly remains of potential interest, both as therapy and as a biomarker. Another potential cardiac-derived peptide is relaxin, although the precise role of this local expression is still unresolved.

In the darkness of the bowel resides the largest endocrine system in the human body. With more than 100 known bioactive substances, the endocrine gut is involved in almost every physiological mechanism. From a cardiovascular point of view, most attention has been paid to insulin and later the incretins (which facilitate insulin release). In fact, insulin infusion used to be considered a reasonable treatment of acute myocardial infarction, and the days of glucose–insulin–potassium infusion are not completely over. The cardiac myocytes express receptors for both insulin and glucagon, and thus they also affect cardiac metabolism and function. Interestingly, both peptides seem to possess independent cardioprotective properties, that is they protect cardiomyocytes from apoptosis under different forms of stress. This cardioprotective aspect will certainly be pursued in the near future, as the need for such adjuvant therapy is overwhelming. In the light of the present interest in incretin, it should not be overlooked that the gut still produces a large number of other bioactive peptides with potential effects on the cardiovascular system.

Finally, other hormonal axes are involved in cardiovascular function and disease. For decades, the pituitary vasopressin (an antidiuretic peptide) has been known to be involved in the heart failure syndrome. Recently, a method for measuring the stable C-terminal copeptin fragment from the vasopressin precursor was introduced and a new marker in heart failure was established. Chromogranins are another example of new possible players in cardiovascular disease, where chromogranin A concentrations in plasma are associated with mortality after infarction, and chromogranin A and chromogranin B even seem to be produced in the heart itself . Last, but not the least, adipokines such as leptin and adiponectin also seem to be important players in cardiovascular disease.

Clinical Endocrinology:

A. Hypertension

Hypertension is so common that it ordinarily falls into the realm of the generalist. Most hypertension is “essential,” meaning that the true cause has not been determined. However, there is increasing information about the mechanisms for hypertension, such that the proportion of patients that fall into the “essential” group is diminishing. It is commonly advantageous to identify the cause of hypertension, because sometimes it can be cured or greatly ameliorated through specific approaches. A number of hormonal disorders can cause hypertension (Table 1). The high incidence of primary aldosteronism is mentioned above. Unlike thinking in the past, it is now known that in most diagnosed patients the serum potassium level is in the normal range. Diagnosis of primary aldosteronism can result in either surgical cure of the hypertension or targeted pharmacotherapy. Patients with an aldosterone-producing adenoma may be treated with unilateral laparoscopic adrenalectomy. Patients with bilateral idiopathic hyperplasia are treated medically, ordinarily using a specific MR blocker. Realization of the need for surgical cure or MR blockade will be increasing with the emerging data showing that aldosterone has deleterious cardiovascular effects independent of its blood-pressure-elevating activities. Thus, it will be insufficient just to treat the blood pressure.

Table1: Endocrine causes of hypertension

Adrenal-dependent
Pheochromocytoma
Primary aldosteronism
Hyperdeoxycorticosteronism
Congenital adrenal hyperplasia
11β-Hydroxylase deficiency
17α-Hydroxylase deficiency
Deoxycorticosterone-producing tumor

Primary cortisol resistance
Cushing's syndrome
Apparent mineralocorticoid excess (AME)/11β-hydroxysteroid dehydrogenase deficiency
Genetic
Type I AME
Type II AME
Acquired
Licorice or carbenoxolone ingestion (type I AME)
Cushing's syndrome (type II AME)
Thyroid-dependent
Hypothyroidism
Hyperthyroidism
Parathroid-dependent
Hyperparathyroidism
Pituitary-dependent
Acromegaly
Cushing's syndrome
Insulin-related
Insulin resistance
Renin-related
Renovascular disease
Renin-secreting tumor
Coarctation of the aorta
Perirenal hematoma (Page kidney)

AME: Apparent Minerelocorticoid excess

Hypertension due to a pheochromocytoma is much more rare (estimated incidence 1.55–8 per million persons per year) than that due to primary aldosteronism [9,10]. It is important to suspect, confirm, localize, and resect pheochromocytomas because: 1) the associated hypertension is curable with surgical removal of the tumor, 2) of the risk of a lethal paroxysm, and 3) at least 10% of the tumors are malignant. Diagnosis is especially important because the hypertension may be most refractory to therapy, and, rarely, if a tumor is present, it may become malignant.

Renovascular hypertension is another curable form whose incidence is increasing with the increased age of the population [11,12]. Surgical therapy or percutaneous transluminal renal artery angioplasty can be curative, and specific therapy with blockade of the renin angiotensin system is, in most cases, beneficial.

The endocrinologist is uniquely skilled at diagnosing these various causes of hypertension. Whereas the means for diagnosing these conditions has improved greatly in recent years, the tests are not always simple, and multiple tests are sometimes required to make a diagnosis.

B. Metabolic syndrome

There are several definitions for metabolic syndrome; the one elaborated by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) is one of the most widely used, confirming the diagnosis in presence of any three of the following five traits:
-Abdominal obesity, defined as a waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in females;
-Blood pressure ≥130/85 mmHg or drug treatment for hypertension;
-Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for hyperglycemia or diabetes;
-Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for hypertriglyceridemia;
-Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females or drug treatment for low HDL cholesterol.
Current treatments involve attacking the individual components, although newer pharmaceuticals such as the thiazolidinediones affect more than one component simultaneously.

C. Obesity

Obesity is increasingly recognized as a pandemic of major proportions and a disorder that is life threatening and not just a cosmetic problem [13]. Endocrinologists are among those currently making great strides to determine the mechanisms for obesity, and a number of specific mechanisms have been identified. As these are better defined, the information will lead to improved therapies. Also, a number of specific therapies are in development. It is also important to note that obesity can signify endocrine disease, as is seen with hypothyroidism and Cushing's syndrome. The clinician must be aware of these in approaching the patient with obesity.

D. Dyslipidemia

Lipid disorders contribute significantly to atherosclerosis. Gradually, management has shifted from total cholesterol to LDL and HDL and onto the additional consideration of other atherogenic species such as lipoprotein (a), homocysteine, and C-reactive protein, reflecting thrombogenic and inflammatory influences on the atherosclerotic processes. Furthermore, the upper limit of tolerability for LDL levels has crept down, such that a much higher proportion of patients have abnormal levels [14,15]. There is also more recent awareness that triglycerides comprise a risk factor for atherosclerosis that is independent of their effects on LDL or HDL[16]. This is especially true for the diabetic patient [16].
Despite advances in means to treat dyslipidemia, treatment is inadequate in many cases, and most patients are not even screened for factors other than total cholesterol, LDL, HDL, and triglycerides. The statins that block cholesterol synthesis and appear to have additional anti inflammatory actions related to the atherogenic processes provide limited effects[17]. Thus, increasingly, patients will be placed on multiple drug regimens. Whereas management of dyslipidemia by necessity will be placed predominately in the hands of primary-care physicians, the endocrinologist can play a specific role with patients that are difficult to control with standard regimens and that have unusual phenotypes. As with obesity, it is also remembered that hypothyroidism itself can result in elevations in LDL[18,19]. Cushing's syndrome can also be associated with lipid abnormalities, and clinicians need to look for these conditions when appropriate [20].

E. Thyroid disease

Both hypothyroidism and hyperthyroidism have deleterious effects on the cardiovascular system [18, 19,21,22]. In hypothyroidism, there can be elevations of plasma levels of LDL, hypertension, and poor cardiac contractility leading to exacerbation of heart failure. Hyperthyroidism can lead to hypertension and several cardiac abnormalities. It can precipitate atrial arrhythmias, including atrial fibrillation. It can precipitate or exacerbate angina pectoris and possibly precipitate myocardial infarction. Hyperthyroidism can also lead to heart failure.

Thus, for these and other reasons, management of these disorders is important. In addition, up to 15% of women over the age of 60 have subclinical hypothyroidism, defined as abnormally elevated plasma thyroid-stimulating hormone levels with normal T_4 levels [23,24]. Although the literature is controversial, some studies suggest that this condition leads to elevations of LDL [25], and most endocrinologists feel that these conditions need to be treated as well, especially if there is evidence for dyslipidemia. Furthermore, subclinical hyperthyroidism, defined as a suppressed plasma level of thyroid-stimulating hormone and normal plasma T_4 levels may be associated with an increased incidence of atrial fibrillation[22]. The endocrinologist can play a role in managing these disorders. Whereas in routine cases management of hypothyroidism is relatively straightforward, in many cases the management is more complex. This occurs, for example, in the elderly in whom replacement therapy must be initiated gradually and in patients with subclinical disease for which the criteria for initiation of therapy are less straightforward. Management of hyperthyroidism is more complex. With overt disease, there is the choice between medical therapy *vs.* radioactive iodine or surgery. Therapy in patients with heart failure or severe atherosclerosis is more complex. Most patients with subclinical disease will not progress to overt hyperthyroidism, and the criteria for initiation of therapy are more complex. The endocrinologist can serve a special role in these cases.

F. Cushing's syndrome

The overt form of Cushing's syndrome is easy to recognize, although one of us (J.D.B.) remembers as a medical student the missed diagnosis of Cushing's disease as a presentation of malignant hypertension. Nevertheless, more and more we are diagnosing this condition at early stages in which the clinical presentation is more subtle[26]. Almost all patients with spontaneous Cushing's syndrome have hypertension[27], and, as stated above, these patients may also be obese. Although the means to diagnose and treat this disorder have improved greatly in recent years, the diagnosis of mild Cushing's syndrome remains one of the most difficult diagnostic tasks for the clinical endocrinologist. The endocrinologist can be a valuable resource in sorting out the myriad of clues to diagnose the syndrome and determine the localization of the abnormally functioning tissue (adrenal, pituitary, ectopic).

G. Diabetes and cardiovascular disease

Cardiovascular disease is particularly prevalent in the diabetic patient [16,27]. In these patients, recent studies have indicated that there should be increased stringency in regulating the blood pressure and lipoprotein levels. Furthermore, blockers of the renin-angiotensin system have proved to be particularly helpful in preventing the progression of renal disease. Endocrinologists have traditionally been involved in treatment of diabetes and in consultation with other physicians regarding treatment. Given the need for more stringent control of cardiovascular risk factors in this disorder, endocrinologists are becoming increasingly involved in consultation and management. This involves both blood pressure control and management of hyperlipidemia. As mentioned earlier, hypertriglyceridemia is an independent risk factor for atherosclerosis, and this is particularly true for the diabetic; regimens need to be established to control this parameter as well.

H. Hormone Replacement Therapy

As we have previously discussed, both estrogens and androgens have major effects on the cardiovascular system. As outlined by Drs. Liu, Death, and Handelsman in this issue of *Endocrine Reviews*, there is controversy whether deficiencies of both of these classes of hormones, as occurs after menopause and andropause, result in an increased risk for developing cardiovascular complications. Most clinicians agree that replacement of androgens is indicated in men with testosterone deficiency. The argument for initiating estrogen replacement therapy remains controversial. As discussed earlier, recent studies using estrogen and progestin replacement therapy failed to demonstrate improvement in cardiovascular risk in postmenopausal women, and trials with estrogen alone are ongoing. Because estrogens have complex actions on other tissues, including bone, uterus, breast, and the central nervous system, the decision to initiate estrogen replacement therapy has become more complex. Endocrinologists

can be useful for advising patients and other clinicians in these situations.

I. NAFLD

NAFLD refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation are present. It represents the most common liver disorder in industrialized countries, with a prevalence of 10 to 46% in the United States, and 6 to 35% (median 20%) worldwide. The diagnosis of NAFLD requires evidence (by imaging or histology) of hepatic steatosis and the exclusion of secondary causes of hepatic fat accumulation, including steatogenic medication (*e.g.* corticosteroids, methotrexate, amiodarone), viral infections (*e.g.* hepatitis C), or hereditary disorders (*e.g.* alpha-1 antitrypsin deficiency, Wilson's disease); moreover, daily alcohol consumption must not exceed 30g for men and 20g for women.

While metabolic syndrome is a known risk factor for cardiovascular disease and is common in NAFLD patients, NAFLD itself may be independently associated with cardiovascular disease [28]. The underlying mechanisms linking NAFLD to cardiovascular disease are very complex and involve a number of different pathways, including insulin resistance, endothelial dysfunction, fibrosis, and alterations in gut microbiota [29].

J. Uremic Cardiomyopathy

The burden of cardiovascular disease in patients with end-stage renal disease is significant, with mortality from cardiovascular disease 15 to 30 times higher than the general population. Uremic cardiomyopathy is classically characterized by diastolic dysfunction in association with myocardial fibrosis and left ventricular hypertrophy in patients with chronic kidney disease.

The prevalence of HF in patients with chronic kidney disease populations increases with age, is markedly more common in dialysis patients (prevalence: 31-36%) than in those with normal kidney function (prevalence: 1.8-4.4%), and is inversely proportional to the estimated glomerular filtration rate.

Uremic cardiomyopathy may manifest as a result of hemodynamic overload (both pressure and volume), and a systemic uremic state. Alterations in mineral metabolism, coronary microvascular dysfunction, and the accumulation of substances such as endothelin, parathyroid hormone, tumor necrosis factor alpha, interleukin-1α and interleukin-6, endogenous cardiotonic steroids as cardenolides (oubain and digoxin) and bufadienolides (marinobufagenin and proscillaridin A) contribute to the pathogenesis of uremic cardiomyopathy [30].

K. HFpEF

Several studies estimate that as many as 40-60% of patients with heart failure (HF) have a normal (≥50%) LVEF [31]. The proportion of patients with HF who have HFpEF is higher in older adults and appears to be increasing by about 1% annually relative to that of HF with reduced ejection fraction (HFrEF) [32] . Most patients with HFpEF display normal left ventricular volumes and evidence of diastolic dysfunction, such as elevated filling pressures at rest or with exertion.

The pathophysiological understanding of HFpEF is still limited. Recent reports have shown that many HFpEF patients exhibit signs of non-resolving inflammation, endothelial dysfunction, insulin resistance, hyperlipidemia, and multiorgan defects [33]. At a cellular level, cardiomyocytes in patients with HFpEF are thicker and shorter than normal cells, collagen content is increased, and recent histologic evaluations have revealed reductions in myocardial capillary density alongside lymphatic dysfunction [34]. Furthermore, substantial evidence indicates that obesity-related HFpEF may result from increased mineralocorticoid signaling, adipokines imbalance, and neprilysin overactivity [35].

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