Review Article

Cardiovascular Endocrinology: A Game Changing Concept

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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 explore new ways of thinking beyond established hormonal axes, and it shouldn't just focus on discovering new markers of disease or treatment strategies not only clarify existing mechanisms but also reveal novel connections between the cardiovascular system and various blood-borne bioactive substances and their corresponding 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.

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The central organ in the cardiovascular system is the heart itself. In a review known heart-derived hormones, focusing on GDF15, myostatin, and ANP/BNP, and their biology in the cardiovascular system. The TGF-<unk> family includes GDF-15 as a distinct member. In the cardiovascular system, cardiac synthesis and secretion of GDF-15 are substantially increased in various cardiovascular diseases (e.g., heart failure)[1,2] Besides being a valuable serum biomarker for cardiovascular disease, recent findings indicate that GDF-15 secreted by the heart also hinders pediatric body growth by inhibiting liver growth hormone signaling, thus functioning as a heart-derived hormone[3]. Myostatin is another member of the TGF-ß 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 demonstrated a positive correlation between plasma myostatin levels and the heart disease biomarker N-terminal pro-BNP in congestive heart failure patients. Additionally, in acute myocardial infarction, myostatin levels were associated with infarct size, suggesting its potential as a biomarker for these heart conditions. 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 relaxing, 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 widespread and often falls within the domain of general medical practice. While most cases are deemed "essential" with an undetermined cause, advancements in understanding hypertension mechanisms have reduced the proportion of patients falling into this category. Identifying the underlying cause is beneficial, as specific approaches can sometimes lead to a cure or significant improvement in hyper- tension. A number of hormonal disorders can cause hypertension (Table 1). As mentioned earlier, there is a high incidence of primary aldosteronism. Contrary to past beliefs, it is now recognized that in the majority of diagnosed patients, the serum potassium level falls within the normal range. The diagnosis of primary aldosteronism can lead to either surgical cure of hypertension or .targeted pharmacotherapy. Aldosterone- producing adenoma patients may undergo unilateral laparoscopic adrenalectomy, while those with bilateral idiopathic hyperplasia are typically treated medically, often with a specific mineralo-corticoid receptor 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. Treating blood pressure alone may be inadequate in addressing the overall management of the condition.

Table1: Endocrine causes of hypertension

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
Parathyroid-dependent
Hyperparathyroidism
Pituitary-dependent
Acromegaly
Cushing"s syndrome
Insulin-related
Insulin resistance
Adrenal-dependent
Pheochromocytoma
Primary aldosteronism
Hyperdeoxycorticosteronism
Congenital adrenal hyperplasia
11ß-Hydroxylase deficiency
17α-Hydroxylase deficiency
Deoxycorticosterone-producing tumor
Primary cortisol resistance
Cushing"s syndrome
Apparent mineralocorticoid excess (AME)/11ß-hydroxysteroid dehydrogenase deficiency
Renin-related
Renovascular disease
Renin-secreting tumor
Coarctation of the aorta
Perirenal hematoma (Page kidney)

AME: Apparent Mineralocorticoid 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]. Suspecting, confirming, localizing, and resecting pheochromocytomas is crucial due to several reasons: 1) Surgical removal of the tumor can cure associated hypertension, 2) There is a risk of a lethal paroxysm, and 3) At least 10% of these 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 provide a cure, and specific therapy involving blockade of the renin-angiotensin system is generally beneficial in most cases.

B. Metabolic syndrome

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) provides one of the most widely used definitions for metabolic syndrome. The diagnosis is confirmed with the presence of any three of the following five traits:

- Abdominal obesity or we can define as waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in females;
- Blood pressure ≥130/85 mmHg or medicinal treatment for hypertension;
- Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or medicinal treatment for hyperglycemia or diabetes;
- Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or medicinal 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 actively advancing our understanding of the mechanisms behind obesity, with several specific mechanisms already identified. As these mechanisms become clearer, it holds the promise of enhanced therapies. Notably, various specific treatments are currently in development. Additionally, it's crucial to recognize that obesity can be indicative of endocrine diseases, such as hypothyroidism and Cushing"s syndrome. When approaching the obese patient, the clinician must be aware of these.

D. Dyslipidemia

Lipid disorders contribute significantly to atherosclerosis. Gradually, management has shifted from total cholesterol to LDL and HDL, and now includes additional consideration of other atherogenic species such as lipoprotein (a), homocysteine, and C-reactive protein, atherosclerotic processes are influenced by thrombogenic and inflammatory factors.. 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 advancements in treating dyslipidemia, there is still inadequate treatment in many cases, and a significant number of patients are not screened for factors beyond 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]. In the future, more patients are likely to be prescribed multiple drug regimens for dyslipidemia. While primary-care physicians will predominantly handle the management, endocrinologists can have a specific role in challenging cases or those with unusual phenotypes that are difficult to control using standard regimens. 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]. Hypothyroidism can result in elevated plasma LDL levels, hypertension, and diminished cardiac contractility, exacerbating heart failure. Hyperthyroidism, on the other hand, may cause hypertension and various cardiac abnormalities, including atrial arrhythmias like atrial fibrillation. It can also precipitate or worsen angina pectoris, potentially leading to myocardial infarction. Additionally, hyperthyroidism is associated with the development of 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]. Endocrinologists play a crucial role in managing disorders like hypothyroidism. While routine cases are relatively straightforward, complexities arise in instances such as managing hypothyroidism in the elderly, where replacement therapy needs gradual initiation, and in patients with subclinical disease where criteria for therapy initiation are less clear. Managing hyperthyroidism is inherently more complex. With overt disease, there is the choice between medical therapy and radioactive iodine or surgery. Therapy in patients who have heart failure or severe atherosclerosis is more complicated. The majority of patients with subclinical disease won't progress to overt hyperthyroidism, and the criteria for initiating therapy are more complicated. These cases can benefit from the special role played by the endocrinologist.

F. Cushing's syndrome

The overt form of Cushing"s syndrome is easily recognizable; however, one of us (J.D.B.) recalls, as a medical student, a case where the presentation of Cushing"s disease was initially missed, being mistaken for 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. Despite significant advancements in diagnostic and therapeutic approaches, identifying mild

Cushing"s syndrome remains among the most challenging tasks for clinical endocrinologists. The endocrinologist serves as a valuable resource in deciphering the complex array 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]. Recent studies suggest increased stringency in regulating blood pressure and lipoprotein levels for patients with this disorder. Blockers of the renin-angiotensin system are particularly effective in preventing the progression of renal disease. Endocrinologists, traditionally focused on diabetes treatment, are now increasingly involved in managing cardiovascular risk factors, including blood pressure and hyperlipidemia, due to the need for stricter control in this disorder. It's essential to address hyper-triglyceridemia, an independent risk factor for atherosclerosis, especially in diabetic patients, requiring established regimens for control.

H. Hormone Replacement Therapy

Indeed, as mentioned earlier, both estrogens and androgens exert significant effects on the cardiovascular system. As outlined by Drs. Liu, Death, and Handelsman discuss whether deficiency of both of these classes of hormones is being discussed in this Endocrine reviews issue the risk of developing cardiovascular complications increases after menopause and andropause. While there is consensus among most clinicians regarding the indication for androgen replacement in men with testosterone deficiency, the initiation of estrogen replacement therapy remains a topic of controversy. Recent studies with estrogen and progestin replacement in postmenopausal women showed no cardiovascular risk improvement, and trials with estrogen alone are ongoing. Given the complex actions of estrogens on various tissues, the decision to initiate estrogen replacement therapy has become more intricate. Endocrinologists play a valuable role in advising patients and collaborating with other clinicians in these situations.

I. NAFLD

NAFLD, or non-alcoholic fatty liver disease, is characterized by hepatic steatosis in the absence of other causes for secondary hepatic fat accumulation. It stands as the most prevalent liver disorder in industrialized nations, with a prevalence ranging from 10 to 46% in the United States and a global range of 6 to 35% (median 20%).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.

Metabolic syndrome has a well-known risk factor like CVD (cardiovascular disease) and also in NAFLD patients, but NAFLD itself may be associated with CVD [28]- but the underlying mechanisms o NAFLD a link with CVD remain complex and involve a number of different pathways, including insulin resistance, endothelial dysfunction, fibrosis, and alterations in gut microbiota [29]

J. Uremic Cardiomyopathy

Patients with end-stage renal disease bear a substantial burden of cardiovascular disease, experiencing mortality rates from cardiovascular issues that are 15 to 30 times higher than the general population. Uremic cardiomyopathy is a classic manifestation characterized by diastolic dysfunction, myocardial fibrosis, and left ventricular hypertrophy in individuals 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 uremic cardiomyopathy, with a prevalence ranging from 1.8 to 4.4%, is inversely proportional to the estimated glomerular filtration rate. This condition can manifest due to 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-1<unk> and interleukin-6, endogenous cardiotonic steroids such 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] . In heart failure with preserved ejection fraction (HFpEF), the majority of patients exhibit normal left ventricular volumes and show signs of diastolic dysfunction, such as elevated filling pressures at rest or during 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 the cellular level, patients with heart failure with preserved ejection fraction (HFpEF) often exhibit thicker and shorter cardiomyocytes compared to normal cells. There is an increase in collagen content, and recent histologic assessments have identified reductions in myocardial capillary density along with lymphatic dysfunction. [34]. Furthermore, substantial evidence indicates that obesity-related HFpEF may result from increased mineralocorticoid signaling, adipokines imbalance, and neprilysin overactivity [35] .

Conclusion

In summary, historical and recent discoveries revealed the importance of the endocrine function of the heart. Studies of various heart-derived hormones highlighted their shared fundamental features and pointed to a unified endocrine mechanism that the heart uses to communicate with the rest of the body. The answers to many exciting basic and translational questions will further advance the field of cardiac endocrinology.

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