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Neurocardiology: Therapeutic Implications for Cardiovascular Disease

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SUMMARY

The term “neurocardiology” refers to physiologic and pathophysiological interplays of the nervous and cardiovascular systems. This selective review provides an update about cardiovascular therapeutic implications of neurocardiology, with emphasis on disorders involving primary or secondary abnormalities of catecholamine systems. Concepts of scientific integrative medicine help understand these disorders. Scientific integrative medicine is not a treatment method or discipline but a way of thinking that applies systems concepts to acute and chronic disorders of regulation. Some of these concepts include stability by negative feedback regulation, multiple effectors, effector sharing, instability by positive feedback loops, allostasis, and allostatic load. Scientific integrative medicine builds on systems biology but is also distinct in several ways. A large variety of drugs and non-drug treatments are now available or under study for neurocardiologic disorders in which catecholamine systems are hyperfunctional or hypofunctional. The future of therapeutics in neurocardiology is not so much in new curative drugs as in applying scientific integrative medical ideas that take into account concurrent chronic degenerative disorders and interactions of multiple drug and non-drug treatments with each other and with those disorders.

Keywords

Autonomic nervous system; dysautonomia; neurocardiology; norepinephrine; sympathetic nervous system

Introduction: What is Neurocardiology?

“Neurocardiology” refers to physiological and pathophysiological interplays of the nervous and cardiovascular systems. Neurocardiology is therefore essentially interdisciplinary.

Neurocardiology is evolving as a discipline in clinical medicine. From initial emphases on behavior patterns in coronary artery disease [1] and the role of stress in hypertension [2], the

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Conflict of Interest

The authors have no conflict of interest.

field has by now expanded greatly to include many primary or secondary hyperfunctional and hypofunctional abnormalities of catecholamine systems (Table 1) that relate importantly to cardiovascular therapeutics.

This review is not and cannot be comprehensive. The main purpose is not to describe in detail diagnostic and therapeutic strategies for each of the numerous common and rare neurocardiologic disorders but to convey a conceptual framework. The reader will find that large subject areas such as metabolic syndrome, cardiorenal failure, and dialysis-related cardiovascular morbidity, all of which include neurocardiologic facets, receive barely any mention. Instead, several disorders have been chosen to exemplify particular principles of scientific integrative medicine as applied to neurocardiology.

Catecholamine Systems and Neurocardiologic Disorders

In humans, the endogenous catecholamines are norepinephrine (NE), epinephrine (EPI), and dopamine (DA). NE is the main neurotransmitter mediating cardiovascular regulation by the sympathetic nervous system and is a major neurotransmitter in the central nervous system. EPI is the powerful chemical effector of the adrenomedullary hormonal system. DA is a key central neurotransmitter, is released with NE during sympathetically mediated exocytosis [3], and is an auto-paracrine effector [4].

Catecholamines not only can precipitate acute events such as stress cardiopathy [5] and emotion-related sudden death [6] but also contribute to chronic conditions such as metabolic syndrome [7] and hypertension [8,9]. Progressive degenerative loss of catecholamine neurons in the brain and periphery underlies the movement disorder and dysautonomia that characterize Parkinson disease (PD) [10,11].

Concepts of Scientific Integrative Medicine

Scientific integrative medicine is not a treatment method or discipline but a way of thinking that applies systems concepts to understand clinical disorders. Multiple simultaneous degenerations combined with effects of multiple drugs and remedies and myriad interactions between the degenerations and the treatments constitute the bulk of modern medical practice. The scientific integrative medicine approach provides a framework for understanding highly complex and dynamic challenges to our integrity as organisms and in turn for developing novel treatments based on this complexity and dynamism [12].

Negative Feedback Regulation

Physiological homeostatic systems entail negative feedback regulation of numerous monitored variables, including core temperature, blood pressure, serum osmolality, glucose levels, and metabolic rate. Conceptually, each system depends on a comparator—a *homeostat*—to compare afferent information about the monitored variables with set points or other criteria for responding (Figure 1).

Disruption of a negative feedback loop, by preventing afferent information from reaching the brain, inability to process the information and regulate effector functions correctly, or

dysfunction or loss of effectors, increases fluctuations in levels of monitored variables [13]. Positive feedback loops are inherently unstable, and conversion from a negative to a positive neurocirculatory feedback loop presages rapid decompensation. For instance, one can understand transitions from heat stress to heat shock and from compensated to decompensated heart failure in terms of positive feedback loops.

Multiple Effectors

Multiple effectors regulate levels of most monitored variables of the body (Figure 2). Having available multiple effectors extends the range of control, allows at least some regulation of the monitored variable if a particular effector fails (compensatory activation), and enables elaboration of specific, adaptive effector patterns. Thus, the sympathetic noradrenergic system, adrenomedullary hormonal system, and hypothalamic–pituitary–thyroid axis are effectors for regulation of core temperature, and hypophysectomy, thyroidectomy, and hypothyroidism all activate the sympathetic noradrenergic system compensatorily [14,15].

Compensatory activation of sympathetic nerves in the heart can for long periods be a major source of homeostasis in the face of intrinsic cardiovascular degeneration. Eventually, however, the same activation can induce neurocirculatory positive feedback loops, resulting in cardiovascular instability, rapid worsening of clinical status, and death. Associations of poor prognosis with a high rate of appearance of NE in the coronary sinus (cardiac NE spillover), a large arterial-cardiac venous increment in plasma NE, or decreased uptake and increased washout of cardiac ^{123}I-metaiodobenzylguanidine-derived radioactivity occur in diverse disorders including congestive heart failure [16,17], ventricular arrhythmias [18], dilated cardiomyopathy [19], diabetes mellitus [20], metabolic syndrome [21], and chronic renal failure [22] and fit with this notion.

Effector Sharing

Different homeostatic systems can share effectors (Figure 3). Sharing of the adrenomedullary hormonal system by the barostat and glucostat can explain hyperglycemia in any of several emergencies such as hemorrhagic shock [23], stroke [24], sepsis [25], and myocardial infarction [26]. Not surprisingly, treatment of hyperglycemia by insulin infusion in these situations does not improve outcome. Analogously, sharing of the vasopressin system by the barostat and osmostat can explain hyponatremia in heart failure [27,28]. From the principle of effector sharing one may predict that the most efficient means to reverse hyperglycemia and hyponatremia in these conditions is to treat the underlying cause.

Stress, Allostasis, and Allostatic Load

The “homeostat” theory defines stress as a condition in which expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match current or anticipated perceptions of the internal or external environment, and the discrepancy elicits patterned, compensatory responses [12]. One can conceptualize stress in terms of an error signal that reflects the difference between afferent information about conditions as sensed and a set point for responding that is determined by a regulator [29], as shown in Figure 4.

Steady state levels of monitored variable can be modified by changing the set point or other instructions for responding. *Allostasis* refers to this "other sameness." The flexibility comes at the cost of wear and tear—*allostatic load* (Figure 4). Allostatic load can lead eventually to a positive feedback loop and rapid system failure.

By way of analogy, suppose you went on sabbatical for a year and that when you left you forgot to close a large window in your home. The temperature would be controlled at the programmed settings, but the air conditioner would be on more in the summer and the furnace would be on more in the winter. With these appliances being on more of the time there would be more wear and tear on them, and they would eventually become less efficient. This means they would be on more of the time, and this would accelerate the wear and tear—a positive feedback loop. In fact, when you returned, you might find that the entire heating and cooling system had failed. According to the notion of allostatic load, it is by way of prolonged activation of effectors to maintain allostasis that chronic stress can contribute to the development of chronic degenerative diseases.

Applications to Neurocardiologic Disorders

Heart Attack and Sudden Death

Patients with acute myocardial infarction have a high risk of lethal arrhythmias, reflecting activation of catecholamine systems both as compensatory responses to decreased cardiac pumping efficiency and as autonomic concomitants of distress. High circulating EPI levels and augmented NE release from cardiac sympathetic nerves increase ventricular automaticity. EPI decreases serum potassium levels [30], adding to arrhythmogenicity.

Takotsubo Cardiopathy

Takotsubo cardiomyopathy refers to a relatively recently described form of acute, reversible cardiomyopathy in which apical akinesia gives the heart the shape of a *takotsubo*, a Japanese fishing pot for trapping octopus [31]. *Takotsubo* cardiomyopathy occurs with relatively high incidence in elderly women soon after exposure to severe emotional distress [5]. Symptoms mimic acute myocardial infarction; however, coronary angiography fails to demonstrate coronary occlusion. The condition can trigger sudden cardiac failure or death, yet in survivors cardiac function typically normalizes within a few weeks. Some patients seem susceptible to repeated episodes. This is an area of current research.

Takotsubo cardiomyopathy features remarkably high plasma catecholamine levels [5] and depressed cardiac contractile function. Proposed pathogenetic mechanisms include coronary microvascular spasm (resulting at least partly from coronary sympathetic nervous activation) and cardiotoxicity from neuronal NE and hormonal EPI [31], which may interact to precipitate multiple positive feedback loops.

Heart Failure

Heart failure entails markedly increased cardiac sympathetic nerve traffic [32] and therefore increased delivery of NE to myocardial cells. High local catecholamine levels promote ventricular hypertrophy and predispose to arrhythmias. Both increased wall stiffness and

arrhythmias worsen the heart's pumping efficiency, in turn reflexively evoking further increases in sympathetic nerve traffic to the heart—a positive feedback loop.

Catecholamine increases the work of the heart. In a patient with coronary stenoses, the rate of oxygen utilization may exceed that of oxygen delivery via coronary perfusion. Lack of oxygen delivery to the sympathetic nerves themselves in the heart tends to make their storage vesicles "leaky," augmenting NE release even for the same rate of sympathetic nerve traffic [33].

Increased sympathetic nervous system outflows augment cardiac filling because of decreased venous capacitance, direct and indirect sodium-retaining effects, and increased total peripheral resistance. Cardiac overfilling leads to accumulation of fluid in the lungs, producing hypoxemia, acidemia, and distress, all of which stimulate catecholamine systems, worsening cardiac overfilling. As noted above for *takotsubo* cardiopathy, acute severely increased catecholamine levels can decrease rather than increase cardiac pumping efficiency, precipitating a rapidly life-threatening positive feedback loop manifesting in fulminant pulmonary edema.

Not surprisingly, in congestive heart failure the plasma NE level constitutes an independent prognostic factor and correlates with functional status [34,35].

Hyponatremia occurs commonly in heart failure. One way to conceptualize the basis for this association is from sharing of the vasopressin/anti-diuretic hormone (ADH) effector by two homeostats, the barostat and the osmostat. Decreased efficiency of cardiac ejection releases the vasopressin system from baroreflex restraint, and vasopressin levels in the bloodstream increase. Because of increased vasopressin levels, the kidneys retain "free water," and serum osmolality and serum sodium concentrations fall. The most appropriate treatment for hyponatremia attending heart failure is not hypertonic saline (which could precipitate pulmonary edema) or water restriction but alleviation of the heart failure.

Hypertension

The principle of multiple effectors can help explain the perennial controversy about the role of the sympathetic noradrenergic and adrenomedullary hormonal systems in the development and maintenance of essential hypertension [9,36,37]. Multiple effectors determine blood pressure, and disruption of sympathetic outflow to study its pathophysiological role leads to compensatory activation of the other effectors.

Researchers have debated for many years whether baroreceptor "debuffering" increases "resting" blood pressure—that is, whether debuffering produces a form of neurogenic hypertension. Increased sympathetic outflow to the kidneys seems to be a major determinant of the renal function curve that relates natriuresis to renal perfusion pressure [38,39]. Release of renal sympathetic outflow from baroreceptor restraint could lead to a long-term increase in blood pressure by resetting the renal function curve and compensatorily activating the renin–angiotensin–aldosterone system.

Two recent developments involve devices rather than drugs to treat chronic hypertension. One is based on afferent baroreflex activation and the other on renal sympathetic

denervation. Chronic carotid sinus electrical stimulation produces sustained decreases in blood pressure in hypertensive dogs, even during adrenergic blockade [40]. Clinical trials of a carotid sinus stimulator for resistant hypertension are currently under way. A recent acute study of hypertensive patients reported a rapid depressor response to carotid stimulation that was associated with sympathoinhibition [41]. Although muscle sympathetic nerve activity decreased sharply beginning soon after the start of the stimulation, sympathetic activity subsequently increased toward baseline. A catheter-based system for radiofrequency ablation of renal sympathetic innervation has been introduced, also for resistant hypertension [42]. This approach is derived from substantial preclinical literature that renal sympathetic nerves contribute to sodium retention and blood pressure especially during stress. Renal adrenergic stimulation augments activity of the renin– angiotensin–aldosterone system, and in the central nervous system angiotensin modulates baroreflex regulation of renal sympathetic neural outflow [43]. Given the multiplicity of effectors regulating blood pressure one may predict substantial interindividual variability and complex determinants of efficacy of both these devices.

Baroreflex Failure

In humans, baroreceptor “debuffering” by surgical denervation or local anesthesia of the carotid sinus area increases blood pressure acutely and concurrently increases values for indices of sympathetic nervous system activity. Irradiation-induced arterial baroreceptor denervation, while predisposing to episodes of paroxysmal hypertension and very high plasma NE levels, does not necessarily produce sustained hypertension [13]. On the other hand, as noted above carotid sinus electrical stimulation produces chronic decreases in blood pressure in hypertensive dogs.

Patients with orthostatic hypotension (OH) in the setting of chronic autonomic failure typically have supine hypertension, which can be quite severe. In general, drugs that raise blood pressure during orthostasis worsen supine hypertension, posing a major therapeutic challenge. OH in such patients is associated with baroreflex-cardiovagal and baroreflex-sympathoneural failure. Conversely, because of inability to modulate release of NE reflexively from sympathetic nerves, baroreflex failure likely is a key determinant of OH. In addition, patients with pure autonomic failure or Parkinson disease with orthostatic hypotension have evidence for loss of cardiac and extra-cardiac noradrenergic innervation, which likely interacts with baroreflex failure to produce OH. Dysfunctional baroreflexes might also contribute to deleterious sympathetic stimulation in heart failure [44].

Beginning in the early 1980s, attempts were made to develop a “prosthetic baroreceptor” that could prevent or ameliorate OH by controlled i.v. infusion of NE [45]. More recent case reports have noted sometimes spectacular improvement in orthostatic tolerance by patient-controlled i.v. infusion of pressors without continuous pressure monitoring [46]. Development of a pharmacologic or electronic [47] system to modulate or replace baroreflexes would be a major step forward for treating combined OH with supine hypertension and possibly heart failure [48].

Primary Neurocardiologic Disorders

Pheochromocytoma—The clearest evidence for a role of high circulating levels of catecholamines in clinical hypertension comes from patients with pheochromocytoma, rare tumors of catecholamine-synthesizing cells. Despite their rarity, pheochromocytomas are important in medicine, for two reasons. First, the tumors typically are benign, and surgical removal of a pheochromocytoma can cure the hypertension. Second, in response to seemingly minor perturbations such as anesthesia induction, pheochromocytomas can release their catecholamine contents into the bloodstream, resulting in paroxysms of high blood pressure or acute heart failure that can be lethal.

Because of the commonness and nonspecificity of symptoms and signs of pheochromocytoma, such as hypertension that is difficult to control, headache, anxiety, pallor, sweating, fast pulse rate, and palpitations, and the potentially catastrophic consequences of missing the diagnosis, clinicians frequently attempt to exclude pheochromocytoma, despite its rarity. In such patients, the most sensitive screening test is plasma free metanephrines [49].

Pheochromocytoma provides an experiment of nature for learning about long-term consequences of high catecholamine levels. These include not only myocardial hypertrophy but also dilated cardiomyopathy. Removal of the tumor can be lifesaving and reverse even dilated cardiomyopathy [50].

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)—Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a primary inherited arrhythmia syndrome that often manifests as episodes of syncope in the first or second decade of life and predisposes to unexplained sudden cardiac death in young adulthood. Mutations of genes encoding voltage gated ion channels (channelopathies) underlie a predisposition to ventricular arrhythmias in response to endogenous catecholamines. In particular, mutations of the gene for ryanodine receptor RYR2 account for about 70% of the CPVT cases and cause the autosomal dominant form of the disease [51,52]. It is thought that the mutation leads to disruption of intracellular Ca^{2+} homeostasis, with cAMP-induced aberrant Ca^{2+} release from the sarcoplasmic reticulum into the cytoplasm. β-Adrenoceptor activation, which increases cAMP generation, may therefore precipitate a pathogenic positive feedback loop in which ventricular arrhythmia rapidly increases cardiac sympathetic and adrenomedullary hormonal system outflows, in turn exacerbating aberrant Ca^{2+} release.

Because symptoms and signs are likely to be brought on by emotional or physical stress, clinical evaluation by echocardiography or electrocardiography in the resting state can yield false negative results. Other disorders predisposing to sudden cardiac death in young adulthood include congenital long QT syndrome and Brugada syndrome.

β-Adrenoceptor blockers are a mainstay of treatment for CPVT. An automated defibrillator may have to be implanted. Treatment for CPVT also includes left sympathectomy. Such treatment leaves open the theoretical possibilities of denervation supersensitivity of cardiac adrenoceptors and compensatory activation of the adrenomedullary hormonal system;

however, plasma levels of catecholamines have not been assessed in CPVT with or without therapeutic cardiac denervation.

Primary Chronic Autonomic Failure—Failure of the sympathetic noradrenergic system causes a fall in blood pressure when the patient stands up—orthostatic hypotension (OH). Sympathetic nervous system failure also produces postprandial hypotension, exercise-related hypotension, a tendency to relatively slow pulse rate, exercise intolerance, and fatigue.

Most physicians lump together all forms of autonomic failure. In contrast, the current presentation distinguishes orthostatic or postprandial symptoms and hemodynamic abnormalities as manifestations specifically of failure of sympathetic noradrenergic function.

Using cardiac sympathetic neuroimaging one can now distinguish pathophysiological subtypes of autonomic failure. PAF and PD+OH are invariably associated with severe loss of sympathetic nerves in the left ventricular myocardium. In contrast, most patients with multiple system atrophy (MSA) have intact sympathetic innervation. These findings have led to a clinical pathophysiological classification of neurogenic OH [53] and to somewhat different treatment regimens.

Pure Autonomic Failure—PAF features persistent, consistent OH in the absence of signs of central nervous system disease and other known causes of OH. In PAF, OH results from generalized loss of sympathetic noradrenergic nerves coupled with baroreflex failure. Because of the loss of noradrenergic nerves, drugs that release NE, such as tyramine, yohimbine, amphetamine, and ephedrine, produce relatively small increases in blood pressure compared to drugs that directly stimulate adrenoceptors, such as midodrine and phenylephrine. Patients with PAF can have large, beneficial increases in blood pressure in response to adrenoceptor agonists, consistent with “denervation supersensitivity” [54].

Multiple System Atrophy—MSA is a progressive neurodegenerative disease that involves dysregulation of multiple components of the autonomic nervous system and lesions of multiple central neurotransmitter systems [55]. Most MSA patients have OH. In MSA, OH usually reflects loss of ability to modulate sympathetic nerve traffic to intact nerve terminals. This is a major difference from PAF or PD+OH. MSA patients typically have deficient orthostatic increments in plasma NE levels, a feature shared with PAF and PD+OH.

Parkinson Disease with Orthostatic Hypotension—Autonomic failure and OH occur fairly commonly in PD and can come on early in the disease course [56,57]. Studies during the past decade have found consistently that all patients with PD+OH have cardiac sympathetic denervation. PD+OH patients also have evidence of extra-cardiac sympathetic noradrenergic denervation [58,59]. The combination of cardiac and extra-cardiac sympathetic denervation with baroreflex failure probably explains OH attending PD.

Because most patients with PD who do not have OH nevertheless have at least some loss of cardiac sympathetic nerves [60], PD appears to be not only a movement disorder but also a form of dysautonomia. Cardiac sympathetic denervation can precede the movement disorder

by several years [61], providing a potential biomarker to detect the pathogenetic process in at-risk individuals and to track effects of putative neuroprotective agents.

Cardiac denervation in PD+OH might produce symptoms such as fatigue and dyspnea on exertion that mimic mild heart failure.

Controversial Neurocardiologic Disorders—Many different diagnostic appellations have been suggested for psychoneurocardiologic syndromes. The length of the list probably indicates not so much the variety of conditions as ignorance about pathophysiological mechanisms.

Postural Tachycardia Syndrome—Patients with the postural tachycardia syndrome (postural orthostatic tachycardia syndrome, POTS) have an excessive increase in pulse rate during standing, usually without OH. The finding of OH does not exclude a diagnosis of POTS, however, as delayed OH [62] can occur. Patients with POTS have several nonspecific symptoms, such as chronic fatigue, heat intolerance, exercise intolerance, headache, chest pain, palpitations, disturbed sleep, decreased ability to concentrate (“brain fog”), and a tendency to panic or anxiety in threatening situations.

Researchers have thought that the tachycardia in POTS reflects increased cardiac sympathetic nerve traffic in compensation for decreased venous return to the heart or inadequately increased total peripheral resistance when the patient stands up. Either abnormality could disinhibit cardiac sympathetic outflow from baroreflexive restraint.

There are many potential causes for an excessive orthostatic decrease in venous return to the heart. The possibilities of blood volume depletion or excessive dependent pooling of blood have drawn particular attention. Consistent with excessive blood pooling in the legs, pelvis, or lower abdomen during orthostasis, inflation of a military antishock trousers suit reduces substantially the increase in heart rate in response to orthostasis in patients with POTS.

In “partial dysautonomia” or “neuropathic POTS” it is thought that there is a patchy loss of sympathetic innervation, such as in the legs or abdominal organs [63]. When the patient stands up, the blood would pool because of failure of the arterioles or veins to constrict, and the sympathetic nervous system supply to the heart would be stimulated reflexively. POTS may also be a manifestation of dysfunction of the renin–angiotensin–aldosterone system, a major system regulating sodium balance and extracellular fluid volume [64]. Rarely, POTS can result from failure to inactivate NE by reuptake via the cell membrane NE transporter [65].

In “hyperadrenergic orthostatic intolerance,” the problem is thought to be a primary abnormality in the functioning or regulation of the sympathetic nervous system itself. In a related syndrome, the “hyperdynamic circulation syndrome,” the patients have a fast pulse rate all the time, variable high blood pressure, increased heart rate responses to the drug isoproterenol, and increased plasma NE and EPI levels at rest and during provocative maneuvers [66,67]. β-Adrenoceptor blockers or benzodiazepines improve the syndrome. It is unclear whether patients with this syndrome have an increased frequency of later development of established hypertension.

In “inappropriate sinus tachycardia,” the heart rate is increased substantially even during supine rest. Radiofrequency ablation of the sinus node is considered for patients with inappropriate sinus tachycardia who are resistant to treatment with medications.

Neurocardiogenic Syncope—Neurocardiogenic syncope (vasovagal syncope, reflex syncope, neurally mediated hypotension, the common faint) is the most common cause of sudden loss of consciousness in the general population. Patients with frequent neurocardiogenic syncope can feel unwell between episodes, with an inability to tolerate prolonged standing, chronic fatigue, headache, and heat intolerance, as in POTS.

Neurocardiogenic syncope typically involves a particular evoked neuroendocrine pattern of central neural origin. EPI levels are high at the time of the acute episode [68,69], while activity of the sympathetic noradrenergic system is not as increased—“sympathoadrenal imbalance” [70,71]. Bradycardia can be prominent, indicating stimulation of parasympathetic cardiovagal outflow; however, heart transplant recipients can faint [72,73], and cholinergic blockade fails to prevent neurocardiogenic syncope, indicating that the neurally mediated hypotension does not depend solely on increased vagal tone. Studies have disagreed remarkably as to whether skeletal muscle sympathetic outflow falls abruptly [74–77] or is maintained [78]. Although EPI-induced relaxation of blood vessels in skeletal muscle could decrease vascular resistance in skeletal muscle and in the body as a whole, non-selective β-adrenoceptor blockade is not universally effective in preventing tilt-induced neurocardiogenic syncope [79]. Neurocardiogenic syncope is attended by other neuroendocrine changes, including elevated levels of β-endorphin [80], atrial natriuretic peptide, corticotropin, and vasopressin [81,82].

It therefore appears that there are multiple determinants of the hypotension that characterizes fainting [83]. Experimental attempts to elucidate contributions of these determinants by blocking effectors may yield false negative results because of compensatory activation of alternative effectors.

Non-Drug and Drug Treatments for Catecholaminergic Neurocardiologic Disorders

Clinical neurocardiologic disorders are often treatable. In this section, treatments are divided into non-drug, drugs for hyper-catecholaminergic states, and drugs for hypo-catecholaminergic states.

Non-Drug Treatments

Elevation of the Head of the Bed—In patients with OH, elevation of the head of the bed at night improves the ability to tolerate standing up in the morning. Because such patients typically have supine hypertension [84], mechanisms of this benefit probably include decreased pressure natriuresis.

Salt Intake—High salt intake tends to increase extracellular fluid volume. Clinicians usually recommend a high salt diet for patients with chronic orthostatic intolerance or OH. Normally when a person takes in a high salt diet, the kidneys increase the amount of salt in

the urine, and this limits the increase in blood volume. Drugs that promote retention of sodium by the kidneys, such as fludrocortisone, are usually required for high salt intake to increase body fluid volume and blood pressure effectively.

Meals—Eating a large meal leads to shunting of blood toward the gut. Patients with chronic orthostatic intolerance or with OH therefore usually are advised to take frequent small meals.

Compression Hose—Compression hose or other compression garments tend to decrease the amount of orthostatic pooling of blood in veins. This can decrease leakage of fluid from the veins into the tissues and decrease pedal swelling. In patients with veins that fill up or leak excessively during standing, compression garments can improve toleration of prolonged standing. In patients with OH, the problem may be less with the veins than with the arteries and arterioles. Wearing compression garments therefore may be disappointing in the management of OH.

Temperature—Patients with dysautonomias often have an inability to tolerate extremes of external temperature. When exposed to the heat, patients with failure of the sympathetic nervous system may not sweat adequately to maintain the core temperature by evaporative heat loss. Patients with chronic orthostatic intolerance, such as from postural tachycardia syndrome (POTS), can have heat intolerance because of loss of blood volume by sweating or shunting of blood away from the brain. When exposed to cold, patients with sympathetic nervous system failure may not constrict blood vessels adequately in the skin, so that the body temperature falls (hypothermia).

Exercise—As a person exercises, arterioles tend to relax, due at least partly to the accumulation of byproducts of metabolism. The sympathetic nervous system normally counters this tendency. Activation of sympathetic nerves to the heart during exercise increases the force and rate of the heartbeat, and the cardiac output increases. Patients with sympathetic neurocirculatory failure are thought to have a decreased ability to increase the cardiac output during exercise, producing a decrease in blood pressure, shortness of breath, or early exhaustion.

Patients with inadequate sympathetic responses feel worse after than during exercise, probably because of cessation of muscle pumping. It is important for such patients to stay hydrated and avoid activities like eating a large meal or driving in a hot car after exercise.

Pacemakers and Sinus Node Ablation—Insertion of a cardiac pacemaker can prevent fainting in patients with neurocardiogenic syncope or POTS. This is an area of active research and some controversy, because a low pulse rate at the time of fainting might not cause and might even be the result of low blood flow to the brain. In patients with POTS and chronic fatigue, a pacemaker may not alleviate fatigue.

Patients with “inappropriate” sinus tachycardia may undergo therapeutic sinus node ablation. This is helpful if the tachycardia does not reflect compensation via cardiac

sympathetic stimulation for another problem such as hypovolemia; eliminating the compensation would make the patient worse.

Neurosurgery—Some patients with chronic orthostatic intolerance have brainstem anatomic change called Chiari malformation, in which the cerebellar tonsils lie below the foramen magnum. Neurosurgery can correct the malformation, but the orthostatic intolerance does not necessarily disappear. This is a controversial topic; patients should seek a second opinion before submitting to this procedure.

Bilateral thoracic sympathectomies or sympathotomies are done for refractory palmar hyperhidrosis [85–87]. Iontophoresis, botulinum toxin injection, and glycopyrrolate cream are alternatives. Because sweating is mediated mainly by sympathetic cholinergic fibers, autonomic neurosurgery is usually effective; however, a variety of expected and unexpected consequences can result, including ectopic (e.g., plantar) hyperhidrosis, gustatory sweating, Horner syndrome, and decreased heart rate responses to exercise. The latter seems to be related to partial cardiac denervation [88]. Anecdotally, fatigue, altered mood, blunted emotion, and decreased ability to concentrate can develop after bilateral thoracic sympathectomies.

Drug Treatments—In this section, drug treatments of neurocardiologic disorders are classified in terms of therapy for hypercatecholaminergic and hypocatecholaminergic states.

Hypercatecholaminergic

Clonidine—Clonidine is an α2 adrenoceptor agonist that acts in the central nervous system to decrease sympathetic nervous system outflows and in the periphery at presynaptic receptors to decrease NE release from sympathetic nerve terminals [89]. Therefore, even though clonidine stimulates a type of α-adrenoceptor, clonidine normally decreases blood pressure.

Clonidine usually causes drowsiness and often causes a dry mouth. Sedation from clonidine has limited its clinical use.

Clonidine normally decreases plasma NE levels. In patients with pheochromocytoma plasma NE can be increased because of release of NE into the bloodstream independently of the sympathetic nervous system. In such patients failure of clonidine to reduce plasma NE constitutes a positive diagnostic test result [90,91]. Conversely, the combination of a high plasma NE level and a large fall in blood pressure in response to clonidine may identify patients with “hypernoradrenergic hypertension” [92]. In such patients, clonidine can be very effective in lowering the blood pressure. Clonidine is also effective in treating withdrawal from addictive drugs and in treating panic disorder.

Adrenoceptor Blockers—α-, β-, and combined α- and β-adrenoceptor blockers are used commonly to treat hypercatecholaminergic states such as POTS. Although β-adrenoceptor blockers reliably decrease heart rate, they do not necessarily alleviate other symptoms of POTS such as fatigue, “brain fog,” and exercise intolerance. Nonselective β-adrenoceptors

have been disappointing in preventing neurocardiogenic syncope and can even prolong asystole in the cardioinhibitory form of the condition [79].

In pheochromocytoma, treatment of hypertension with β-blockers alone is contraindicated, because this leaves unopposed α-adrenoceptor occupation by circulating NE. β-Adrenoceptor blockers are effective for hyperdynamic circulation syndrome [67].

β-Adrenoceptor blockers can precipitate pulmonary edema in patients with acute heart failure. On the other hand, β-blocker treatment of cardiomyopathy can reduce long-term morbidity and morbidity, possibly by attenuating cardiac hypertrophy and decreasing predisposition to arrhythmias from sympathetic stimulation.

Imidazoline Receptor Agonists—Clonidine is an imidazoline. Research comparing clonidine with α-methyl-norepinephrine, which like clonidine is an α2 adrenoceptor agonist, led to the discovery of a class of imidazoline receptors, stimulation of which decreases sympathetic noradrenergic outflows. An endogenous clonidine-displacing substance—agmatine [93]—and the synthetic drugs moxonidine (Physiotens) and rilmenidine exemplify imidazoline I_1 receptor agonists. Moxonidine decreases blood pressure and sympathetic outflow [94]. A trial of moxonidine in patients with symptomatic heart failure and reduced ejection fraction was stopped due to excessive early mortality in the moxonidine treated group [95]. This adverse outcome might have reflected recruitment of cardiac sympathetic outflow to maintain cardiac performance in the setting of intrinsic myocardial dysfunction, so that blocking the compensatory activation was deleterious. Moxonidine is available in several countries but has not been approved by the US FDA.

α-Methyl-Para-Tyrosine—α-Methyl-*para*-tyrosine (metyrosine, Demser) competitively antagonizes tyrosine hydroxylase, the rate-limiting enzymatic step in catecholamine biosynthesis. Plasma levels of DOPA, NE, dihydroxyphenylacetic acid, and dihydroxyphenylglycol decrease [96]. α-Methyl-*para*-tyrosine is used to decrease catecholamine biosynthesis in patients with pheochromocytoma prior to surgery [97]. Because of inhibition of catecholamine synthesis, the drug produces depressed mood and parkinsonism as long-term side effects [98].

Carbidopa—Carbidopa, which is combined with levodopa in Sinemet, inhibits decarboxylation of levodopa to DA outside the brain. Although carbidopa effectively inhibits L-aromatic-amino-acid decarboxylase, attained plasma L-DOPA concentrations are so high (about 10,000 nmol/L) that plasma levels of the DA metabolite dihydroxyphenylacetic acid typically increase by more than 20-fold (from about 7 to about 180 nmol/L), implying that patients taking levodopa/ carbidopa actually have substantially increased production and metabolism of DA outside the brain.

Ganglion Blockade—Ganglion blockers such as trimethaphan (TRI) and pentolinium (PEN) interfere with ganglionic transmission by blocking neuronal acetylcholine receptors. These drugs produce symptoms and signs of both parasympathetic and sympathetic failure, including dry mouth, constant pulse rate, decreased sweating, fixed pupils, and OH. Plasma NE levels fall [99] to a greater extent than do plasma dihydroxyphenylglycol levels [100],

consistent with ongoing NE turnover due to net leakage from vesicles into the neuronal cytoplasm.

Ganglion blockers are not used to treat hypercatecholaminergic states, because the drugs always produce OH. They are used for research purposes, to evaluate the contribution of sympathetic innervation to blood pressure. Patients with MSA have large declines in blood pressure during ganglion blockade, revealing a post-ganglionic sympathoneural contribution to supine hypertension in this disease [101], whereas patients with PAF have small declines, due to sympathetic post-ganglionic denervation.

Reserpine and Tetrabenazine—Reserpine is a classical drug derived from the root of the *Rauwolfia serpentina* (Indian snakeroot) plant. A highly lipophilic drug, reserpine enters monoaminergic neurons and chromaffin cells and irreversibly blocks the type-1 and type-2 vesicular monoamine transporters. By blocking vesicular recycling, reserpine administration rapidly increases net leakage of NE from vesicles into the cytosol and therefore depletes sympathoneural NE stores [102].

After reserpine administration, increased oxidative deamination of cytosolic NE catalyzed by monoamine oxidase results in increased formation of dihydroxyphenylglycol (DHPG), and so plasma DHPG levels at first increase [103]. Subsequently, as vesicular NE stores become depleted, plasma DHPG decreases to low levels. Although reserpine is an effective antihypertensive agent, it is rarely used clinically because of side effects such as depression, orthostatic hypotension, diarrhea, and hypothermia.

Tetrabenazine also inhibits vesicular recycling of monoamines. Because it depletes DA stores it is used to treat hyperkinetic movement disorders such as chorea, tics associated with Tourette's syndrome, and tardive dyskinesias [104]. The drug might prove useful for hyperadrenergic states and offers a better safety profile than reserpine.

Hypocatecholaminergic

Fludrocortisone—Fludrocortisone (Florinef), a synthetic mineralocorticoid that closely resembles the body's main salt-retaining steroid, aldosterone, is used widely to treat chronic orthostatic intolerance and OH. For fludrocortisone to work requires that the patient be on a high-salt diet. The patient gains "fluid weight," and blood pressure increases. Because of the tendency of fludrocortisone to waste potassium, fludrocortisone can cause a fall in the serum potassium level, and so patients taking fludrocortisone should have periodic checks of their serum potassium level.

Fludrocortisone given for OH can cause or worsen high blood pressure when the patient is lying down. The clinician must then balance the long-term increased risk of stroke, heart failure, or renal failure against the immediate risk of fainting or falling from OH.

Midodrine—Midodrine (Proamatine) is a vasoconstrictor that works by stimulating α-adrenoceptors in blood vessel walls. Midodrine is used frequently for neurogenic OH [105]. By stimulating α-adrenoceptors directly, midodrine acts like synthetic NE. In patients with

OH associated with sympathetic noradrenergic denervation, denervation supersensitivity can render midodrine very effective in raising blood pressure.

In using midodrine to treat elderly men with OH, the clinician should be aware that stimulation of α-adrenoceptors can worsen symptoms and signs of prostate hypertrophy, such as urinary retention, urgency, and decreased urinary stream. α1-Adrenoceptor blockers are effective in treating benign prostatic hypertrophy, and such drugs interfere with midodrine.

Somatostatin—Somatostatin (Octreotide) has been reported to be helpful for orthostatic and postprandial hypotension [106]. The drug is expensive and must be injected.

Vasopressin—Vasopressin (or Desmopressin, which is 1-desamino-8-D-arginine vasopressin) sprayed into the nostrils can exert a systemic pressor effect.

Amphetamines—Amphetamines such as methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) can be effective to treat symptoms of chronic fatigue syndrome such as fatigue and decreased ability to concentrate [107]. Methylphenidate has been reported to increase plasma EPI but not NE levels [99], whereas amphetamine increases plasma NE levels [79]. The potential for addiction or abuse limits clinical use of these drugs. It is reasonable to propose that such drugs might be effective for chronic orthostatic intolerance or OH; however, no controlled studies have been done for this sort of application.

Pyridostigmine—Pyridostigmine (Mestinon) is an inhibitor of acetylcholinesterase. The drug therefore increases delivery of endogenous acetylcholine to muscarinic and nicotinic receptors. The latter effect augments ganglionic neurotransmission, and via increased postganglionic sympathetic noradrenergic outflows, blood pressure increases. A potential therapeutic advantage of pyridostigmine to treat OH is that the drug may increase blood pressure more during orthostasis, when sympathetic outflow is increased, than during supine rest [108].

Yohimbine—Yohimbine exerts effects opposite to those of clonidine. Yohimbine increases sympathetic neural outflows and blocks α2-adrenoceptors on sympathetic nerve terminals, thereby increasing plasma NE levels [109]. Yohimbine challenge testing can assess whether a patient with neurogenic OH has releasable NE stores [110], which can be a target for treatment. Yohimbine challenge testing can also reveal excessive NE release in patients with anxiety or panic disorder. In patients with neurocardiogenic syncope yohimbine can improve orthostatic tolerance [76]. Yohimbine administration evokes large increases in blood pressure and plasma NE levels in patients with MSA [111], which can be useful in differential diagnosis from PAF and PD+OH [112] and might improve orthostatic tolerance [113].

Tyramine—Indirectly acting sympathomimetic amines such as dextroamphetamine and tyramine release NE from sympathetic nerve endings and increase plasma NE levels. These drugs are substrates for both the cell membrane norepinephrine transporter (NET) and

vesicular monoamine transporter (VMAT). Probably by intravesicular alkalinization they enhance NE leakage from storage vesicles into the axoplasm. They also interfere with the efficiency of the NET, resulting in transport of the axoplasmic NE into the extracellular fluid. In humans, infusion of tyramine or dextroamphetamine therefore increases plasma NE levels [114,115]. During tyramine infusion, plasma DHPG levels increase more than do plasma NE levels [116], probably because of buildup of NE in the axoplasm.

Foodstuffs such as hard cheeses and red wines contain large amounts of tyramine. Normally dietary tyramine is metabolized in the gastrointestinal tract and liver before the amine can enter the systemic circulation. In patients taking an MAO inhibitor, tyramine is able to reach the sympathetic nerve terminals, and after neuronal and vesicular uptakes of tyramine paroxysmal hypertension can result from release of vesicular NE—a phenomenon termed the “cheese effect” [117]. Because of the susceptibility to severe hypertension due to the cheese effect MAO inhibitors have not had wide usage as antidepressants, despite their clinical efficacy. Intentional combination of tyramine with an MAO inhibitor can be used to treat neurogenic OH [118].

Contamination of TYR infusates with DA can increase plasma DA levels artifactually [119,120]. During infusion of relatively uncontaminated TYR, individual values for changes in plasma DA concentrations are positively correlated with those in NE [3], consistent with a neuronal source of plasma DA.

Isoproterenol—Infusion of the β-adrenoceptor agonist isoproterenol (ISO) increases plasma NE levels [121,122]. The increases probably reflect a combination of agonist occupation of β2-adrenoceptors on sympathetic nerves [123] and reflexive stimulation of sympathetic outflows in response to systemic vasodilation. Patients with chronic autonomic failure associated with generalized sympathetic noradrenergic denervation have attenuated plasma NE responses to infused ISO [58].

COMT Inhibitors (Entacapone)—Entacapone (Comtan) is an inhibitor of catechol-*O*-methyltransferase (COMT). Because levodopa is a catechol, entacapone treatment inhibits metabolic breakdown of levodopa to 3-methoxytyrosine [124]. Treatment of PD with levodopa/carbidopa/entacapone (Stalevo) is becoming increasingly common. In humans, entacapone does not increase peak plasma DOPA concentrations but does increase the area under the curve for DOPA concentrations vs. time [125,126]. Addition of entacapone to levodopa/carbidopa is therefore thought to be potentially beneficial in patients with PD and the “on-off” phenomenon.

ENT does not appreciably affect plasma levels of catecholamines [127], likely reflecting the relatively minor effects of nonneuronal uptake and *O*-methylation on the fate of NE released from sympathetic nerves. On the other hand, ENT augments cardiac responses to infused EPI and ISO, and the drug combination can precipitate ventricular arrhythmias [128].

MAO Inhibitors—Monoamine oxidase (MAO) figures much more prominently in the metabolic fate of DA and NE than does COMT, because sympathetic nerves do not express COMT. Plasma levels of dihydroxyphenylacetic acid, the main deaminated metabolite of

DA, and of dihydroxyphenylglycol, the main deaminated metabolite of NE, therefore exceed by far those of the corresponding *O*-methylated metabolites.

There are two isoforms of MAO, MAO-A and MAO-B. Sympathetic nerves express MAO-A, whereas most extraneuronal cells express both MAO-A and MAO-B. Clorgyline selectively inhibits MAO-A, and selegiline (Deprenyl, Eldepryl) and rasagiline selectively inhibit MAO-B. Because of the MAO-B selectivity, selegiline and rasagiline are not associated with the "cheese effect." MAO-B inhibitors are used commonly in adjunctive treatment of PD. The drugs do not appear to worsen OH [129].

NET Inhibitors—Tricyclic antidepressants, cocaine, and amphetamines inhibit the cell membrane NE transporter (NET). Effects of these agents on plasma levels of NE and its metabolites are complex, because these drugs all enter the brain and can affect sympathetic neuronal outflows.

Desipramine, a classical tricyclic anti-depressant, inhibits skeletal muscle sympathetic nerve traffic and decreases NE spillover in the body as a whole, the forearm, and the kidneys [130]. In contrast, desipramine increases plasma EPI levels, indicating differential effects on sympathetic noradrenergic and adrenomedullary outflows [131]. NET inhibition also decreases plasma dihydroxyphenylglycol levels, an effect that has been attributed to decreased NE turnover [132]. Desipramine abolishes plasma dihydroxyphenylglycol responses and augments plasma NE responses to yohimbine [132].

In humans, intra-nasal cocaine increases blood pressure substantially. After taking into account baroreflexive sympathoinhibition, skeletal muscle sympathetic outflow is increased [133]. In cocaine addicts, i.v. cocaine increases plasma NE and EPI levels [134].

Duloxetine, atomoxetine, and reboxetine are non-tricyclic antidepressants that block the NET. In humans, duloxetine increases plasma NE levels and reduces the plasma DHPG:NE ratio [135]. Reboxetine does not affect plasma NE levels during supine rest [136], possibly because of counter-balancing effects of reuptake inhibition and decreased sympathetic neuronal outflow [137]. Reboxetine decreases plasma DHPG levels [138]. Amitriptyline also tends to increase plasma NE and decrease plasma DHPG levels, consistent with some NET inhibition [138].

L-DOPS—L-threo-3,4-dihydroxyphenylserine (L-DOPS), a NE pro-drug, is an investigational agent for neurogenic OH.

After L-DOPS administration, plasma NE levels increase [139] but by surprisingly little and insufficiently to increase blood pressure [140]. In contrast with small increases in plasma NE levels, there are robust increases in plasma DHPG and dihydroxymandelic acid (DHMA) levels. The pressor response to L-DOPS therefore seems mainly to reflect actions on adrenoceptors within tissues by NE that has escaped extensive metabolic breakdown by MAO and COMT and has not yet reached the systemic circulation.

Water Drinking—A relatively recently described tactic to increase blood pressure in patients with autonomic failure is for them to drink 16 ounces of water [141]. Why water

drinking should increase blood pressure in patients with autonomic failure, when doing so does not affect the blood pressure of healthy people, remains unclear. Water drinking increases standing and postprandial blood pressure in patients with MSA [142].

Patients with chronic orthostatic intolerance often bring a water bottle to the clinical encounter. They sip repeatedly during the day. This habit might indicate a tendency to dehydration and low blood volume, but this notion has not been tested.

The Future: Early Detection and Individualized Prevention

The future of therapeutics in neurocardiology is not so much in new curative drugs as in applying scientific integrative medical concepts that take into account concurrent development of chronic degenerative disorders and interactions of multiple drug and non-drug treatments with each other and with those disorders.

Autotoxicity of Cysotolic Monoamines

Current concepts about mechanisms of PD emphasize pathologic accumulation of α-synuclein, oxidative injury, impaired proteasomal or mitochondrial functions, neuroinflammation, or abnormal kinase signaling [143]. These concepts do not readily explain relatively selective, severe depletion of DA in the putamen compared to other neurotransmitters and other extranigral projection areas.

A potential explanation comes from the notion that cytoplasmic metabolites in catecholaminergic terminals are autotoxins that are produced continuously because of ongoing net leakage of catecholamines from vesicular stores. Catecholamines in the neuronal cytoplasm undergo enzymatic oxidative deamination catalyzed by monoamine oxidase to form catecholaldehydes (dihydroxyphenylacetaldehyde (DOPAL) from DA, dihydroxyphenylglycolaldehyde from NE), which are cytotoxic [144,145], as predicted by Blaschko more than a half century ago [146]. DOPAL has been shown to destroy dopaminergic neurons and cells [144,147] and to evoke precipitation of α-synuclein [148], which in catecholaminergic neurons is a characteristic neuropathological feature of PD [149]. Ongoing production of catecholaldehydes might increase susceptibility of catecholaminergic neurons, and in the nigrostriatal system greater buildup of DOPAL in the putamen than caudate might help explain relatively more severe DA depletion in the putamen [150].

If evidence accrued supporting the notion that aldehydes produced from deamination of cytosolic monoamines (serotonin and NE) constitute a determinant of not only central neural but also cardiac pathology [151–153], the therapeutic implications would be clear: drug treatments to decrease such deamination, directly via monoamine oxidase inhibition or indirectly via augmenting vesicular sequestration, should be neuroprotective.

Compensatory Activation and Timing of Intervention

The timing and rapidity of system failure from positive feedback loops depend on dynamic interactions between usage experience of the system and built-in manufacturing and design characteristics. Analogously, in the body, the occurrence, timing, and rapidity of progression

of degenerative diseases may depend on interactions between environmental exposures and genetic predispositions. The kinetic model of allostasis and allostatic load provides a nice framework for linking stress, distress, allostatic load, and degenerative diseases.

One practical application of these concepts is using the principle of compensatory activation to decide on the timing of heart valve replacement in chronic aortic or mitral regurgitation. Waiting until the patient has symptoms of heart failure or coronary ischemia is not satisfactory, because already symptomatic patients have prohibitive operative morbidity and mortality; yet premature valve replacement is also not satisfactory, because implanted heart valves have a limited life span. Because cardiac sympathetic outflow increases early in heart failure [154], clinical laboratory assessments of cardiac sympathetic outflow might identify an appropriate time for heart valve replacement, before ventricular filling pressures or volume increase or ejection fraction decreases.

Positive Feedback Loops

In patients with chronic diseases of almost any sort, the “inner world” breaks down eventually; a key way this happens is by development of positive feedback loops. Heart failure stimulates the sympathetic nervous system and renin–angiotensin–aldosterone system, which increases fluid retention, growth of heart muscle, and the work of the heart, worsening the heart failure. Chest pain from coronary ischemia evokes distress, stimulating the adrenomedullary hormonal system and increasing the rate of consumption of oxygen by the heart, worsening the ischemia. OH from failure of the sympathetic nervous system causes lightheadedness, a fall, fracture of a hip, and prolonged bed rest in traction, worsening the OH when the patient tries to get up. A footballer practicing in full uniform in the heat releases epinephrine, which constricts skin blood vessels and augments heat production in the body, producing heat exhaustion, which releases more adrenaline, bringing on heat shock and death. Loss of dopaminergic terminals in the nigrostriatal system in the brain increases pathway traffic to the remaining terminals, accelerating DA turnover and thereby production of toxic by-products of DA metabolism, increasing the rate of loss of DA terminals, manifesting eventually as PD.

Application of kinetic models of allostasis and allostatic load may not only provide a framework for linking stress, distress, allostatic load, and degenerative diseases but also lead to development of effective means to prevent or detect and rapidly abort pathogenetic positive feedback loops. For instance, monitoring skin temperature and blood flow might detect signs of excessive adrenomedullary stimulation soon enough to prevent heat shock in a professional football player.

Complexity

The era of developing single drug treatments to cure single diseases is coming to an end. As populations age, chronic degenerative diseases are becoming more prevalent, and the corresponding societal burdens are expanding. Elderly patients typically have multiple comorbidities, take multiple prescribed drugs and over-the-counter dietary remedies or herbal supplements. The disorders interact with each other, the drugs interact with each other, and the disorders interact with the drugs in ever more complex ways.

Modern computerized methods of data analysis, simulation, and decision-making may be applied to this complexity and advise the clinician about the most effective and least harmful avenues to manage neurocardiologic disorders.

Individualized Medicine

Neurocardiologic disorders of catecholamine systems may provide a powerful spearhead of individualized or personalized medicine, because of the extraordinary ability to pinpoint specific metabolic abnormalities in single patients in the context of a medical systems approach. Rather than development of new drugs for particular neurocardiologic disorders, one may now envision combination drug therapies with individualized optimization that take into account not only comorbidities and drug interactions but also compensatory changes in activities of catecholamine systems. Catecholamine systems also can provide specific biomarker patterns [155], for diagnosis and for monitoring individual responses to treatments.

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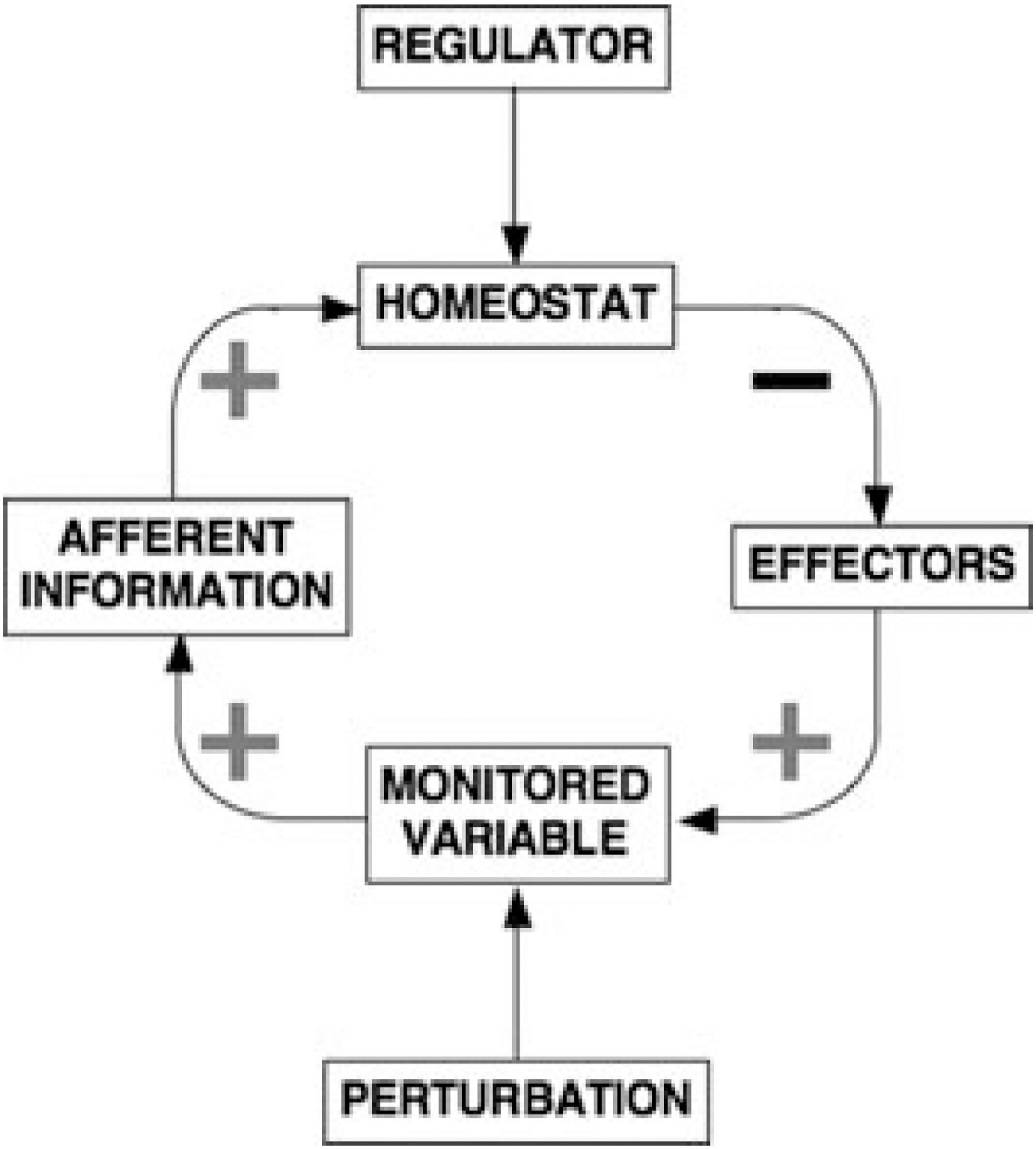

Figure 1.

A physiological homeostatic system. As the level of the monitored variable changes, afferent information is compared with a set point or other algorithm for responding, and the sensed discrepancy leads to altered activities of effectors. Note the odd number of (−) signs, indicating a negative feedback loop. In response to a continuous perturbation, the level of the monitored variable reaches an apparent steady state.

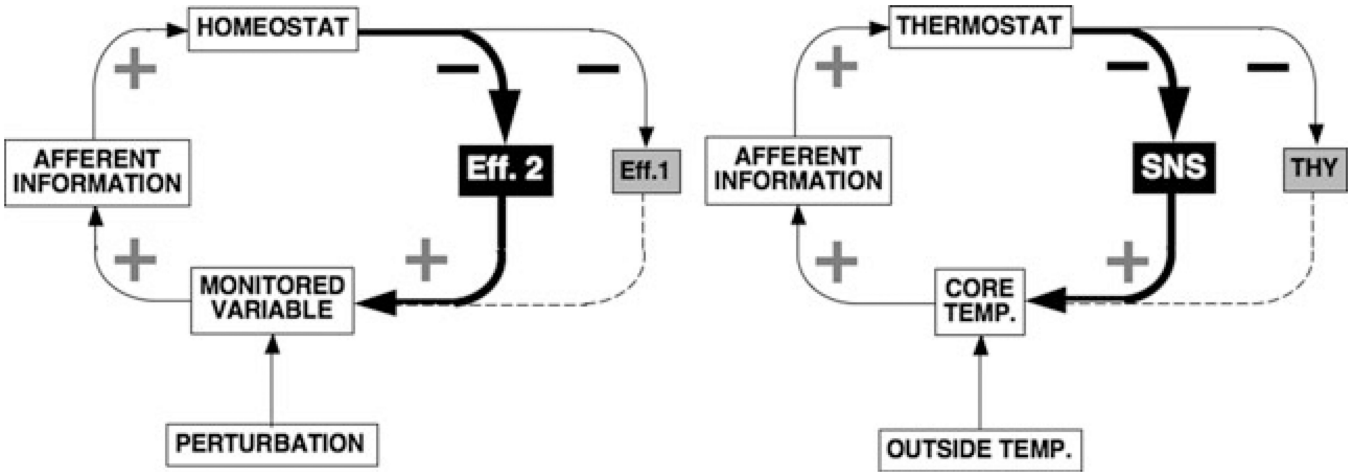

Figure 2.

Compensatory activation. One advantage of multiple effectors is compensatory activation of alternative effectors if one effector fails, enabling control of the monitored variable. For instance, thyroidectomy augments sympathetic nervous system (SNS) responses to cold exposure.

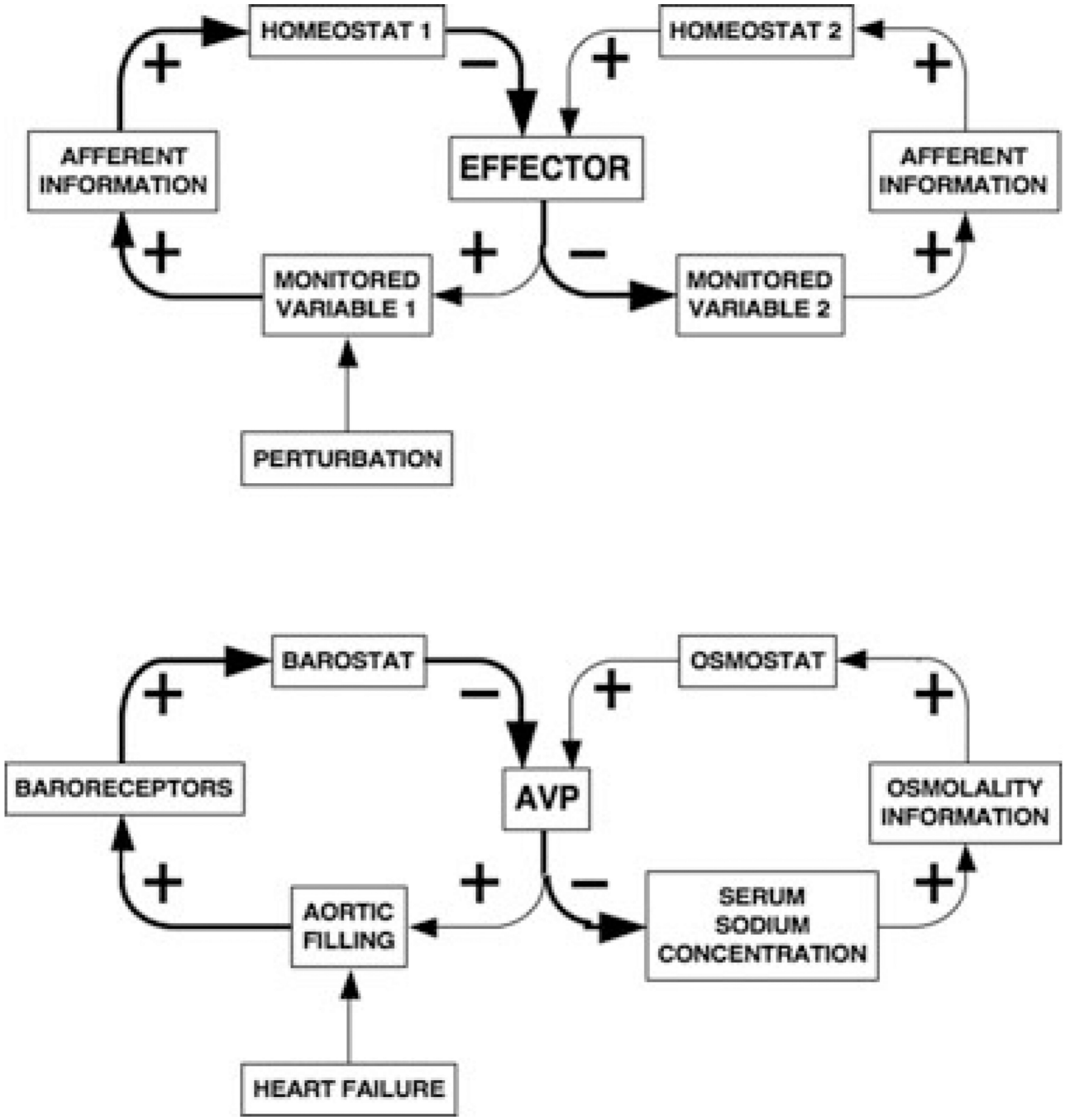

Figure 3.

Effector sharing. Sharing of an effector by multiple homeostats can explain unpredicted consequences and syndromic features of disease processes. For instance, in heart failure, decreased aortic filling increases levels of vasopressin (AVP), which, as the anti-diuretic hormone, promotes retention of free water, explaining hyponatremia attending heart failure.

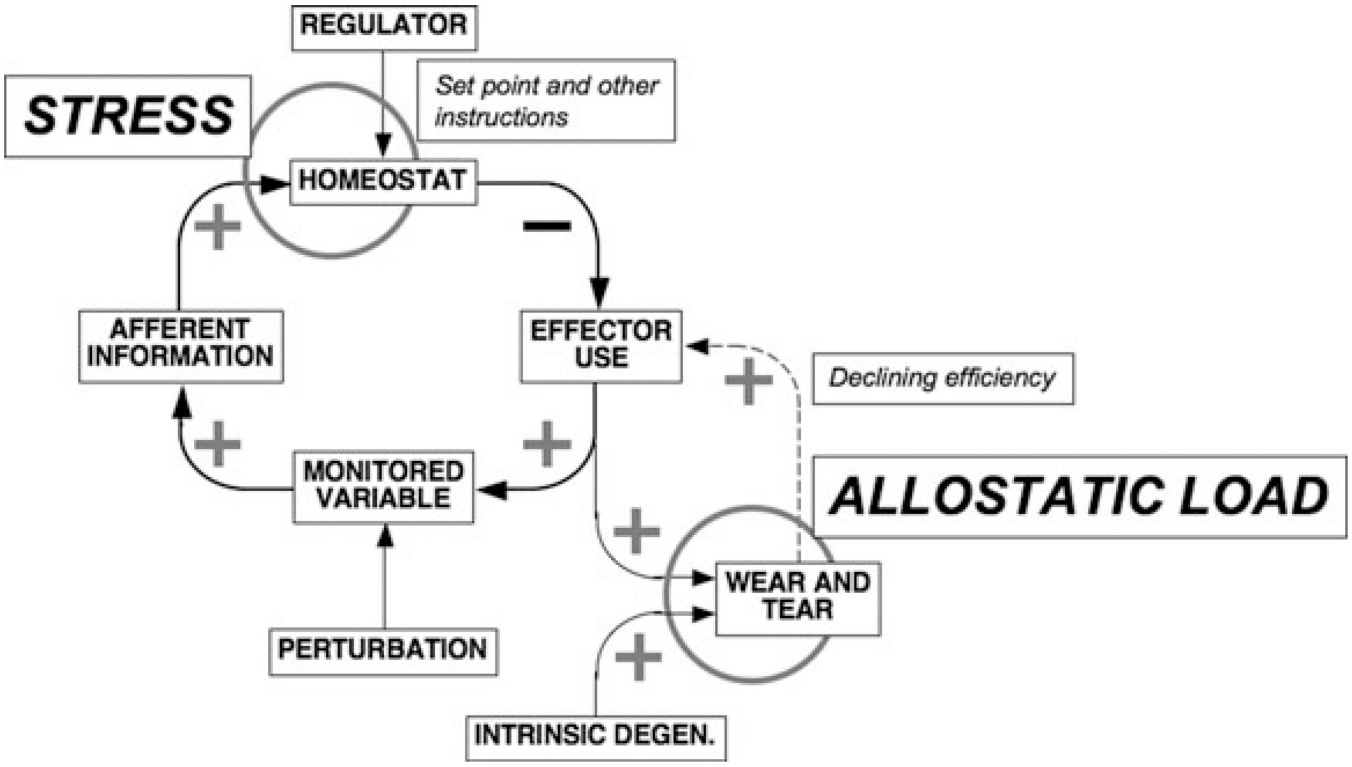

Figure 4.

Homeostatic definitions of stress and allostatic load. In stress the organism senses a discrepancy between afferent information about a monitored variable and a set point and other instructions for responding, altering activities of effectors to decrease the discrepancy. Allostatic load reflects wear and tear, which, if sustained and substantial enough, decreases effector efficiency, further activating the effector and accelerating wear and tear. Allostatic load can therefore eventuate in a destabilizing and pathologic positive feedback loop.

Table 1

Neurocardiologic disorders that feature abnormal catecholaminergic function

Disorders in which physiologic changes in catecholaminergic system function worsen an independent pathologic state
Cardiovascular
Myocardial ischemia and infarction
Arrhythmias
Angina pectoris
Coronary spasm
Heart failure
Generalized and cardiac sympathoneural activation
Myocardial norepinephrine depletion
Prognosis
Arrhythmias and sudden death
Catecholaminergic polymorphic ventricular tachycardia (CPVT)
Psychiatric
Depression
Panic/anxiety
Renal disease
End stage renal disease
Chronic renal failure
Endocrine/metabolic
Hypothyroidism
Obesity, diabetes, and “Metabolic Syndrome”
Disorders where abnormal catecholaminergic function is etiologic
Hypofunctional states without central neurodegeneration
Acute, primary
Neurocardiogenic syncope
Spinal cord transection
Acute pandysautonomia
Sympathectomy
Acute, secondary
Drug-related (e.g., alcohol, tricyclic antidepressant, chemotherapy, opiate, barbiturates, benzodiazepines, sympatholytics, general anesthesia)
Seizures
Guillain–Barre syndrome
Alcohol
Chronic, primary
Pure autonomic failure
Horner’s syndrome
Familial dysautonomia
Carotid sinus syncope
Adie’s syndrome
Dopamine-β-hydroxylase deficiency

Disorders in which physiologic changes in catecholaminergic system function worsen an independent pathologic state

Sympathectomy

Chronic, secondary

Autonomic failure with peripheral neuropathy

Amyloid polyneuropathy

Hereditary amyloid polyneuropathy

Diabetic neuropathy

Diabetic autonomic neuropathy

Painful diabetic neuropathy

Quadriplegia

Chagas disease

Tabes dorsalis

Hyperfunctional states without central neurodegeneration

Acute, primary

Panic/anxiety

Acute, Secondary

Drug-related (e.g., nicotine, caffeine, cocaine, amphetamine, opiate withdrawal, tyramine “cheese effect”)

Stroke-related myocardial necrosis

Seizures

Guillain–Barre syndrome

Post-endarterectomy

Tetanus

Chronic, primary

Hypertension

Neurogenic hypertension

Baroreflex failure

Pheochromocytoma

Sporadic

Familial

Multiple endocrine neoplasia type II von Hippel–Lindau disease

Neurofibromatosis type I

Carotid body tumor

Hypofunctional states with central neurodegeneration

Multiple system atrophy (MSA)

MSA with sympathetic neurocirculatory failure (Shy–Drager Syndrome)

MSA with isolated parasympathetic failure

Parkinson’s disease with autonomic failure

Neurogenetic diseases

Genetic diseases with specific catecholaminergic phenotypes: synthesis

Tyrosine hydroxylase deficiency

Dihydropteridine reductase deficiency

L-DOPA-responsive dystonia

L-Aromatic-amino-acid decarboxylase deficiency

Disorders in which physiologic changes in catecholaminergic system function worsen an independent pathologic state
Menkes disease
Genetic diseases with specific catecholaminergic phenotypes: metabolism
Monoamine oxidase deficiency
Pseudopheochromocytoma
Mysterious or controversial entities
Chronic orthstatic intolerance
Postural Tachycardia syndrome (POTS)
Hyperdynamic circulation syndrome
Hyperadrenergic orthostatic intolerance
Mitral valve prolapse-dysautonomia syndrome
Chronic fatigue syndrome
Neurocardiogenic syncope
Neurasthenia
Chronic regional pain syndrome
Reflex sympathetic dystrophy
Fibromyalgia
Posttraumatic stress disorder
Human essential hypertension
“Type A” coronary-prone behavior pattern