The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management

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Esler M. The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. J Appl Physiol 108: 227–237, 2010. First published November 25, 2009; doi:10.1152/japplphysiol.00832.2009.—Sympathetic nervous system responses typically are regionally differentiated, with activation in one outflow sometimes accompanying no change or sympathetic inhibition in another. Regional sympathetic activity is best studied in humans by recording from post-ganglionic sympathetic efferents (multiunit or single fiber recording) and by isotope dilution-derived measurement of organ-specific norepinephrine release to plasma (regional “norepinephrine spillover”). Evidence assembled in this review indicates that sympathetic nervous system abnormalities are crucial in the development of cardiovascular disorders, notably heart failure, essential hypertension, disorders of postural circulatory control causing syncope, and “psychogenic heart disease,” heart disease attributable to mental stress and psychiatric illness. These abnormalities involve persistent, adverse activation of sympathetic outflows to the heart and kidneys in heart failure and hypertension, episodic or ongoing cardiac sympathetic activation in psychogenic heart disease, and defective sympathetic circulatory reflexes in disorders of postural circulatory control. An important goal for clinical scientists is translation of knowledge of pathophysiology, such as this, into better treatment for patients. The achievement of this “mechanisms-to-management” transition is at differing stages of development with the different conditions. Clinical translation is mature in cardiac failure, knowledge of cardiac neural pathophysiology having led to introduction of β-adrenergic blockers, an effective therapy. With essential hypertension, perhaps we are on the cusp of effective translation, with recent successful testing of selective catheter-based renal sympathetic nerve ablation in patients with resistant hypertension, an intervention firmly based on demonstration of activation of the renal sympathetic outflow. With psychogenic heart disease and postural syncope syndromes, knowledge of the neural pathophysiology is emerging, but clinical translation remains for the future.

norepinephrine; stress; hypertension; cardiac failure; orthostatic intolerance

BRIEF HISTORY OF THE SYMPATHETIC NERVOUS SYSTEM

In 1664, the first anatomically correct depiction of the sympathetic nervous system came from Willis (100). To Pour-fois du Petit is credited the first insight into neural control of blood vessel caliber (47) for his 1727 description of dilatation of conjunctival vessels after sectioning of cervical sympathetic nerves. Subsequent histological examination did demonstrate a dense innervation of blood vessel walls, leading Stelling in 1840 (47) to correctly conclude that the vasomotor fibers were in sympathetic nerves that were carried from the central nervous system to the blood vessels. In the mid-nineteenth century, Brown-Sequard, Waller, and Bernard independently built on these observations (47), with demonstration of vasoconstriction with electrical stimulation of the cut nerves and vasodilatation on a nerve section, which indicated that the sympathetic fibers exerted a tonic, vasoconstrictor influence.

Given the occasion of the 2009 Carl Ludwig Distinguished Lectureship and, of course, independently of this, the contributions of Carl Ludwig and his younger colleagues to the early era of cardiovascular neuroscience research need to be acknowledged. I quote from the American Physiological Society monograph Circulation of the Blood. Men and Ideas (47): “The contributions of Ludwig and his school to the physiology of the heart and circulation covered an extraordinary range. A long list is always tedious, but it is difficult in this case to give an idea of the activity of Ludwig’s laboratory without mentioning at least some of the investigators and their work (35). In neurophysiology these included Ludwig’s own discovery of ganglion cells in the interatrial septa (1848), von Cyon and Ludwig on the depressor nerve (1866), von Cyon and Gaskell on the sympathetic fibers (1866), and Ludwig and Dittmar on the vasomotor center (1873).”

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Identification of the sympathetic neurotransmitter proved to be difficult, with claims for epinephrine (21, 64) and a proposed neuroeffector mechanism that involved the hypothetical sympathins I and E, confusing the picture. It was von Euler who definitively demonstrated the sympathetic transmitter to be norepinephrine when, using a number of bioassay systems, he compared the biological actions of extracted sympathetic transmitter from tissues, including splenic artery nerves of cattle and horses, with those of epinephrine and norepinephrine (91). This discovery provided the theoretical background for the development of pharmacological antagonists of the sympathetic nervous system, subsequently used as antihypertensive drugs, and quickly led to the application of neurochemical methods, initially the measurement of norepinephrine excretion in urine (92), now largely obsolete, in efforts to quantify sympathetic nervous system activity in humans.

CONTEMPORARY METHODS FOR STUDYING THE HUMAN SYMPATHETIC NERVOUS SYSTEM

The development of a sympathetic nerve recording technique applicable to humans (clinical microneurography) in 1968 by Hagbarth and Vallbo (46) and the publication of the first sensitive and specific plasma-catecholamine assay, also in 1968, by Engelman et al. (22) were milestones in the field. The application of these neurophysiological and neurochemical methods, and later refinements of them, came to dominate the investigation of sympathetic neural mechanisms in clinical medicine.

Plasma norepinephrine measurements, although providing a useful guide to sympathetic nervous system function, did come to be seen to have substantial limitations. The principal one was that this, or in fact any other, global index of sympathetic nervous function provides no information on the regional patterning of sympathetic nervous responses. This runs contrary to the organization of the sympathetic nervous system. Precise quantification of individual regional sympathetic nervous outflow was needed. This need came to be met by the sympathetic nerve recording technique and by radiotracer-derived measurements of regional norepinephrine spillover to plasma (Fig. 1).

Microneurography

Hagbarth and Vallbo (46) in 1968 reported a method for measuring efferent multifiber traffic in sympathetic nerves. This technique of clinical microneurography, popularized and extensively applied by Wallin and colleagues (92, 93), provided a method for studying nerve firing in subcutaneous sympathetic nerves distributed to skin and the skeletal muscle vasculature. The technique involves insertion of a fine tungsten electrode through the skin, with positioning of the electrode tip in sympathetic fibers of, most commonly, the common peroneal nerve near the head of the fibula. Micrifier recordings of “bursts” of nerve activity, synchronous with the heart beat, are generated in skeletal muscle vascular efferents. More recently, single fiber sympathetic recording has been successfully performed in humans (45, 60, 65).

Regional Norepinephrine Spillover Measurements

A special impetus to the development of techniques for studying the rates of overflow of catecholamines to the circulation was provided by the lack of clinical methods for studying human sympathetic nervous outflow to otherwise inaccessible organs, such as the heart and kidneys. The inapplicability of the neural recording methodology for clinical research on internal organs led to a continuing search for alternative techniques, especially biochemical ones.

Measurement of organ-specific norepinephrine release to plasma (23, 28) became the gold standard. During constant-rate infusion of tritiated norepinephrine, outward flux of endogenous norepinephrine from an organ (regional norepinephrine “spillover”) can be measured by isotope dilution:

\[ \text{regional norepinephrine spillover} = \frac{[(C_V - C_A) + C_A]}{PF} \]

where \( C_V \) and \( C_A \) are the plasma concentrations of norepinephrine in regional venous and arterial plasma, respectively, \( E \) is the fractional extraction of tritiated norepinephrine in transit of blood through the organ, and \( PF \) is the organ plasma flow. With the use of this technique, typical rates of regional spillover of norepinephrine to plasma in healthy humans at rest are as follows: from the heart, 5–25 ng/min; from the kidneys, 40–110 ng/min; from the lungs, 30–120 ng/min; and from skeletal muscle, 50–130 ng/min (23, 28).

HUMAN SYMPATHETIC NERVOUS PATHOPHYSIOLOGY: THE TRANSITION TO CLINICAL CARE

Evidence is assembled below indicating that abnormalities of the sympathetic nervous system are critical for the development of some cardiovascular disorders. These include congestive heart failure, essential hypertension, the disorders of postural circulatory control causing orthostatic syncope, and “psychogenic heart disease,” heart disease that is consequential to mental stress and psychiatric illness. These abnormalities involve persistent activation of sympathetic outflow to the heart and kidneys in heart failure and hypertension (24, 25, 26, 48, 55, 75, 76, 79, 80), either intermittent or ongoing cardiac sympathetic activation in psychogenic heart disease (5, 5a, 32, 97), and faulty sympathetic circulatory reflexes in the disorders of postural circulatory control (40, 52, 53, 61, 68).

The translation of knowledge of pathophysiology such as this into better medical care for patients is an important goal for
clinical scientists. The achievement of this transition, from “mechanisms to medical management,” is at differing stages of development with the different conditions. With cardiac failure, clinical translation is mature, knowledge of cardiac neural pathophysiology having led to the introduction of β-adrenergic blockers (8, 29), an effective form of treatment (74). With essential hypertension, we may be on the verge of effective “mechanisms-to-management” translation, with the successful testing of selective renal sympathetic nerve ablation in patients with severe essential hypertension resistant to pharmacological treatment (59), an intervention based on the demonstration that sympathetic outflow to the kidneys is commonly activated in essential hypertension (24, 25, 79). With psychogenic heart disease and postural syncope syndromes, knowledge of the neural pathophysiology is preliminary only, and any clinical translation remains for the future.

Cardiac Failure

There are three important historical antecedents to contemporary research on sympathetic nervous system function in human heart failure. The first was the observation that the concentration of the sympathetic nervous neurotransmitter, norepinephrine, is reduced in the failing human heart (14). This was usually taken to signify that the heart was sympathetically denervated. The second was the demonstration that the concentration of norepinephrine in peripheral venous plasma was elevated in patients with heart failure (87), which provided evidence that the sympathetic nervous system is activated, although presumably not in the heart. The third key finding was the observation that prognosis in heart failure patients is related to the level of sympathetic activation when the heart, through its sympathetic nervous system, is not sympathetically denervated. Cardiac failure provided the underpinnings of a major misadventure in heart failure therapeutics; β-adrenergic antagonists were held to be specifically contraindicated, whereas adrenergic cardiac stimulators were widely used but eventually proved to increase mortality. A selective reduction in β1-adrenoceptors in failing human myocardium, these being in close proximity to sympathetic nerve varicosities, but normal extrajunctional β2-adrenoceptor numbers suggested to Bristow et al. (8) that the sympathetic nerves of the failing heart must be intact and actually releasing norepinephrine at an increased rate. When this was confirmed with isotope dilution-derived measurements of cardiac norepinephrine spillover (29, 48), Packer, Bristow, and colleagues devised and conducted the first definitive β-adrenergic blocker trial for congestive heart failure, the carvedilol trial (74), which established that chronic β-adrenergic blockade in cardiac failure was lifesaving. Subsequent trials were confirmatory.

Essential Hypertension

For the past three decades, the major focus in high blood pressure research has been the renin-angiotensin system. The proven value of antihypertensive drugs that block this system has led to reduced attention on other blood pressure-raising systems, including the sympathetic nervous system. Despite this, there is now general agreement that overactivity of the sympathetic nervous system commonly initiates and sustains the blood pressure elevation in patients with essential hypertension (26, 30, 42, 44, 45, 51). Rates of norepinephrine spillover from the failing human heart to plasma are sustained at up to 50 times normal in untreated patients (48, 55, 73, 80). The application of organ-specific tracer kinetic techniques using radiolabeled norepinephrine led to the solution for this conundrum by demonstrating that the sympathetic nervous system is preferentially stimulated in severe congestive heart failure (48, 55, 73, 80).

Application of the norepinephrine spillover methodology has demonstrated activation of the sympathetic nervous system in essential hypertension and those with obesity-related hypertension (25, 30, 79). Obesity hypertension is remarkable in that, despite the presence of renal sympathetic activation, surprisingly there is minimal involvement of the sympathetic outflow to the heart; in many obese hypertensive patients, cardiac norepinephrine is actually reduced (79). Multiunit recordings from sympathetic nerve fibers directed to the skeletal muscle vasculature similarly show a doubling or trebling of sympathetic outflow (42, 43, 44, 45, 51, 60, 75). Single fiber sympathetic recording demonstrates increased fiber firing frequencies and multiple firings.
within a cardiac cycle (firing salvoes), not seen in health (45, 51, 60).

The syndrome of neurogenic essential hypertension appears to account for no less than 50% of all cases of high blood pressure. This estimate is based on both the proportion of untreated patients with essential hypertension who have demonstrable sympathetic excitation and the number in whom substantial blood pressure lowering is achieved, and the extent of this lowering, with antiadrenergic drugs. The application of sympathetic nerve recording and norepinephrine spillover methodologies, in multiple studies from different research groups (24, 25, 26, 30, 42, 43, 44, 45, 51, 60, 79), identified activated sympathetic outflow to the skeletal muscle vasculature and kidneys in ~50% of patients, with the caveat that in those more than 60 years of age, regional norepinephrine spillover from the heart and kidneys is typically not increased (26, 30). Sympathetic nervous system activation is evident in both lean and obese hypertensive patients; sympathetic activation demonstrable with microneurography is particularly prominent in the metabolic syndrome and obesity-related hypertension (43, 44, 51). In the heightened sympathetic activation, beyond that of lean hypertensive patients, seen when hypertension is accompanied by obesity, hyperinsulinemia, hyperleptinemia, and obstructive sleep apnea all have been invoked as prime movers, but in reality the precise mechanism remains uncertain (32).

Does this sympathetic activation initiate and maintain the blood pressure elevation, as has been suggested (30)? There is strong evidence to support this claim. Combined α- and β-adrenergic blockade markedly reduces blood pressure in patients with essential hypertension, an effect particularly prominent in obese hypertensive patients (6, 98). Ganglionic blockade lowers blood pressure to the point of near normalization of pressure in obesity-related hypertension (83). In patients with resistant hypertension, responding inadequately to concurrent treatment with multiple antihypertensive drug classes, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and diuretics, radiofrequency ablation of the renal sympathetic nerves lowers blood pressure remarkably (59, 82), as described below.

Neurogenic essential hypertension: research translation. The sympathetic nervous system is the “forgotten pathway” in the treatment of hypertension. Despite the importance of neural pathophysiological mechanisms in pathogenesis, therapy specifically targeting the sympathetic nervous system is currently underutilized. This may soon change with the recent testing of device-based therapies for reducing sympathetic nervous system activity and, as a consequence, blood pressure. One of these is the surgically implantable arterial barostimulator, which operates by continuous electrical stimulation of the carotid sinus buffer nerves (70).

Another revolutionary treatment principle, described in more detail here, which was recently successfully tested in patients with resistant (uncontrolled) hypertension, involves ablation of the renal sympathetic nerves with a radiofrequency-emitting catheter inserted percutaneously into the femoral artery in the groin and advanced to lie, in turn, in the lumen of both renal arteries (59). Sympathetic nerves enter the human kidneys in the walls of the renal arteries, within reach of ablative energy delivery.

In many experimental models of hypertension, the sympathetic outflow to the kidneys is activated, and renal sympathectomy typically prevents the development of the hypertension (19). In earlier times, before the availability of antihypertensive drugs, extensive surgical sympathectomy was used as a treatment of severe hypertension (50, 84); survival benefit was demonstrated, but complication rates were high, as was morbidity from the extensive denervation, which did not specifically target the kidneys.

Initiation of the new treatment strategy for hypertension was based on these observations and the demonstration that the renal sympathetic outflow is activated in essential hypertension (24, 25, 26, 30, 79). For entry into the recently completed trial, patients had to meet international criteria of uncontrolled essential hypertension (clinical blood pressure in excess of 160/90 mmHg on 3 drugs, including a diuretic). In participating hypertensive patients, radiofrequency energy in 90° quadrants was delivered in stepwise fashion to the full circumference of the renal artery wall. The initial aims were to establish that the procedure does produce renal sympathectomy in humans, that it is safe, and that blood pressure is lowered. This seems to have been confirmed (59). To establish whether the catheter ablates renal sympathetic nerves, measurements of renal norepinephrine spillover were made at baseline and at follow-up; results to date indicate that sympathetic denervation does, in fact, occur in most patients, although this is usually incomplete, with the mean fall in renal norepinephrine spillover being 47.5% (P < 0.05). The level of blood pressure reduction achieved, a mean fall of 24/10 mmHg at 3 mo and 29/16 mmHg at 12 mo (P < 0.001), was actually greater than anticipated, but it should be emphasized that in this proof-of-principle trial, the experimental design is not blinded. At this point, in those patients with the longest follow-up (2 yr), blood pressure reduction is sustained, suggesting that renal sympathetic innervation, if it has occurred, is insufficient to cancel out the blood pressure benefit.

Uncertain at present is the importance of destruction of renal afferent nerves in the antihypertensive effect achieved by the radiofrequency ablation procedure. An unexpected observation with the procedure is that sympathetic outflow from the central nervous system (CNS) is reduced (82), as evident in reduced whole body norepinephrine spillover measured by isotope dilution and lowering of sympathetic nerve traffic to the skeletal muscle vasculature measured by microneurography (82). There is conclusive evidence that renal afferent nerves exist and that their projections to the hypothalamus can stimulate sympathetic outflow (11, 54, 58). This CNS input from renal afferent nerves is critical in producing both the sympathetic activation and hypertension found in patients with end-stage renal disease (16, 63). It is probable that radiofrequency deafenentiation of the kidney in the patients with previously resistant hypertension studied in the reported trial contributed to the blood pressure lowering observed.

Postural Circulatory Dysregulation and Syncope

Recurrent unexplained fainting while standing is a common cause of medical referral for specialist care. Standard testing is often unhelpful for diagnosis, leaving the treating physician with little to offer a very disabled patient, at risk of injury or death from falls or motor vehicle accidents during blackouts.
Postural syncope is attributable to disordered neural circulatory control. In a recent review (89), my colleagues and I described the identifiable phenotypes of postural syncope: 1) neural degenerative diseases of the brain (Shy-Drager syndrome and Parkinson’s disease) (37), which impairs the central control of reflex sympathetic outflow, of the peripheral sympathetic nerves (pure autonomic failure) (37, 39, 40, 67, 68), or accompanying long-standing diabetes; 2) postural tachycardia syndrome (POTS), which is characterized by an exaggerated reflex sympathetic nervous response to standing, causing the prototypical tachycardia (52, 61); and 3) neurocardiogenic (vasovagal) syncope, in which the recurrent postural fainting occurs in one of two clinical contexts, either in patients with persistently low systolic blood pressure while supine (70–95 mmHg) or in patients with normal supine pressure and, in fact, no identifying characteristics other than their tendency to faint (89).

The knowledge base for precise diagnosis and treatment has until recently remained very deficient (2, 89). My colleagues and I recently made progress in delineating the neural pathophysiology of these disorders (61) with the concurrent application of methodology involving multiunit sympathetic nerve recording, isotope dilution-derived measurement of norepinephrine spillover to plasma, and the analysis of sympathetic nerve proteins, accessed with a subcutaneous forearm vein biopsy and quantified with Western blotting (Fig. 2). Our results suggest that each disorder has a sympathetic nerve protein “signature;” we plan to evaluate whether analysis of sympathetic nerve proteins can become the primary basis for diagnosis, replacing the cumbersome and unreliable diagnostic tilt-table testing (89).

Illustrative results are provided for the patients with recurrent neurocardiogenic syncope accompanying chronically low blood pressure (Fig. 3). This clinical phenotype encompasses those individuals whose supine systolic blood pressure is at the extreme lower end of the normal range, 70–95 mmHg. This is a common reason for clinical presentation at postural syncope clinics but is often mistakenly discounted as the basis for the syncope. Paradoxically, despite the low blood pressure, sympathetic outflow from the brain registered with multiunit sympathetic nerve recording is elevated (Fig. 3). This contrasts with spillover of norepinephrine to plasma, which is subnormal. An electrochemical dysjunction thus is present in the sympathetic nerves of these patients, in which sympathetic nerve firing is disproportionate to neurotransmitter release. Sympathetic nerve proteins involved in norepinephrine synthesis, vesicular storage, synaptic release, and neuronal reuptake were quantified in an effort to understand this paradox. The sympathetic nerves were accessed via a subcutaneous forearm vein biopsy (61); these veins have a dense sympathetic innervation. Testing was for the abundance in sympathetic nerves of tyrosine hydroxylase, the rate-limiting enzyme for norepinephrine synthesis; VMAT2, the vesicular monoamine transporter that transfers norepinephrine into sympathetic neuronal storage vesicles; dynamin I, critical to release and recycling of vesicles; and the norepinephrine transporter (NET), which captures and returns the transmitter to the sympathetic varicosity after its release (Fig. 3).

Tyrosine hydroxylase was at very low abundance in these patients (~10%), suggesting that the primary pathogenesis is a reduced capacity for norepinephrine synthesis, which is in harmony with the observation that in this postural syncope phenotype, sympathetic nerve firing is increased but transmitter release is subnormal. The primary mechanism, whether mutational or epigenetic in origin, is uncertain.

This finding might now, perhaps, provide the basis for specific, individualized therapy, targeting the demonstrated pathophysiology. Testing will be done for efficacy of the norepinephrine prodrug L-dihydroxyphenylserine (L-DOPS) in the low blood pressure phenotype patients (Fig. 2). L-DOPS is enzymatically converted to norepinephrine by aromatic acid decarboxylase, which is not deficient in these patients. This thinking is analogous to the treatment with L-DOPS of patients with mutational dopamine-β-hydroxylase deficiency (88) who have near-zero capacity for sympathetic neuronal synthesis of norepinephrine but can replenish sympathetic nerve norepinephrine stores with L-DOPS dosing and benefit clinically.

**Psychogenic Heart Disease**

The pathway toward the current recognition (30, 69) that mental stress and psychiatric illness is a cause of cardiovascular disease has been long, halting, and at times vigorously defended by the opposing forces of the medical status quo. The heart-mind medical duality takes many forms (Table 1). The mind-heart causal chain is perhaps best established for heart disease consequential to acute mental stress and to depressive illness (34, 78). The adverse cardiovascular consequences of panic disorder and chronic mental stress are probable but do remain contentious.

“Psychoneurocardiology.” A common theme of this field is the importance of neural mechanisms, particularly those involving the sympathetic nervous system, in the origins of cardiovascular disease attributable to stress and psychiatric illness. Evidence exists affirming the mechanistic importance...
of extreme sympathetic nervous system activation in stress (takotsubo) cardiomyopathy (97), of acute activation of the cardiac sympathetic outflow, in panic attacks accompanied by coronary artery spasm (31, 34, 66, 95), and of chronic activation of the cardiac sympathetic outflow in patients with depressive illness (5a), almost to a level seen in patients with heart failure. Surprisingly, in the field of stress-related cardiovascular disease, it is not cortisol that is the prime mover, unlike in some other medical settings.

Acute mental stress “triggering” of heart attacks. Research linking mental stress to myocardial infarction and sudden death is often disputed because of disagreement over what constitutes a stress. Evidence that rates of sudden, nontraumatic death are markedly increased during earthquakes, with the 1994 Los Angeles earthquake providing a very telling example (62), is free of this criticism. During an earthquake, no doubt everyone is terrified (96).

Are heart attacks during community disasters a special case only or of more general relevance? In a real sense, international football games can be a “community disaster” even if the national side wins! The recently published and already celebrated analysis of acute coronary heart disease clinical presentations in German nationals living in Munich during the 2006 Football Association (FIFA) World Cup demonstrated a dose-response relationship of acute mental stress to cardiac events (94). Heart attacks were more likely on days when the performance of the German team determined their progress toward the final (fewer heart attacks in Munich if Germany was not playing on that day or when the Germany match was a dead rubber, with Germany progression assured) and most likely when the match was particularly gripping, with an uncertain outcome to the end, as in the quarter final match against Argentina decided by penalty shoot-out. Heart attack rates were then lower on the day on which the German team played to determine third and fourth placing (who cares?) and on the day of the final, when Germany was not playing (94).

The biological mechanisms by which acute mental stress triggers heart attacks are now clear (78). First, this occurs most

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![Graph of sympathetic nervous responses to head-up tilting](image)

![Graph of plasma NE spillover](image)

![Western blots of NET, TH, and GAPDH](image)

Fig. 3. Sympathetic nervous responses to head-up tilting in healthy volunteers ($n = 18$) and patients with the low supine systolic blood pressure (LSBP) phenotype of neurocardiogenic syncope ($n = 18$), before the presyncopal event in the patient group. Compared with those of healthy subjects, sympathetic nerve firing rates were elevated during the tilt in LSBP patients ($O; P < 0.01$; top), but in contrast, whole body norepinephrine rate was subnormal in the patient group ($P < 0.02$) during tilting, despite the increased central nervous system sympathetic outflow. I attribute this sympathetic nerve electrochemical dysjunction to impaired norepinephrine synthesis, since TH abundance was reduced in the LSBP patients ($P < 0.05$; bottom). DYN 1 and VMAT2 abundance (not shown) were normal in LSBP patients. NET protein was reduced in the patient group ($P < 0.05$), perhaps an adaptation to reduced norepinephrine synthesis; this abnormality does not explain the low norepinephrine spillover. A conjectural treatment of the LSBP patients with the norepinephrine prodrug L-DOPS is proposed. MSNA, muscle sympathetic nerve activity; NS, normal subjects. [Unpublished findings from an ongoing study with my colleagues, Drs. Gautam Vaddadi, Elisabeth Lambert, and Ling Guo.]
commonly in those with existing atherosclerotic coronary artery narrowing, although this may have been clinically silent and unrecognized. With acute mental stress there is preferential activation of the sympathetic outflow to the heart (27), accompanied by adrenal medullary secretion of epinephrine, which in the presence of coronary artery stenosis and myocardial ischemia can cause ventricular arrhythmias. The attendant blood pressure surge can fissure coronary artery plaques, providing a focus for thrombosis, leading to myocardial infarction. Increased epinephrine secretion activates both platelets and the blood coagulation cascade, predisposing to thrombosis (34, 78). Delineating these biological mediators of heart risk in acute mental stress has provided a potential target for pharmaceutical prevention, to inhibit platelet activation and block adrenergic cardiovascular stimulation. Agreement has been reached that the triggering of myocardial infarction and sudden death by acute mental stress is no longer a hypothetical construct only. It is now proven, is a matter of relevance to the health of the general community, and has led to preventive medical advice being incorporated into national health advisory documents (9).

**Panic disorder.** In individual personal life, “emotional earthquakes” also occur in those with panic disorder. Panic disorder sufferers often fear that they have heart disease, because of the nature of their symptoms, but in the past often have been reassured that this is not the case. My clinical practice of cardiology has generated case material of panic attacks triggering cardiac arrhythmias (atrial fibrillation, ventricular fibrillation), causing coronary artery spasm (documented with coronary angiography), and precipitating myocardial infarction associated with coronary spasm and thrombosis (31, 34, 66). Epidemiological studies affirm the clinical observations that there is an increased risk of myocardial infarction and sudden death in patients with panic disorder (3, 56, 57).

The research of my group indicates that activation of the sympathetic nervous system during panic attacks is the probable mediating mechanism (5, 32, 95). Multifiber sympathetic nerve recording has documented massive stimulation of the sympathetic nervous system during panic attacks (95), accompanied by a surge of epinephrine secretion from the adrenal medulla. Sympathetic nervous tone at rest is normal, but the sympathetic nerves of panic disorder sufferers have been demonstrated to release epinephrine as a cotransmitter (5, 95). This epinephrine in sympathetic nerves of panic disorder sufferers is presumably taken up from plasma during panic attacks or synthesized in situ by the epinephrine-synthesizing enzyme phenylethanolamine-N-methyltransferase, which has been shown in experimental animals to be induced by chronic mental stress (69) and is present in the sympathetic nerves of patients with panic disorder (33). This sympathetic nerve epinephrine cotransmission is potentially a cause of cardiac arrhythmias.

**Takotsubo (stress) cardiomyopathy.** A clinical end point caused by severe acute mental stress totally different from that described above is now increasingly recognized, following the initial description by Sato et al. (81) in 1990. This is a unique form of cardiomyopathy, the “octopus pot” (takotsubo) or “broken heart” syndrome (81, 97) (Fig. 4). What could be more persuasive of the strength of the brain-heart disease link than the appearance on a cardiac catheterization laboratory ventriculogram of a heart with a bulbous, stunned apex but a normally contacting base (hence the origin of the Japanese name, due to

![Takotsubo Cardiomyopathy](Image)

**Fig. 4.** Ventriculogram during diastole and systole showing the distinctive appearance of the left ventricle in takotsubo cardiomyopathy. During systole, the base of the ventricle contracts normally while there is failure of contraction, in fact, distension (apical ballooning) in the remainder of the ventricle. The Japanese name, originating from the first report of the condition (72), derives from the fancied resemblance of the appearance of the left ventricle to a Japanese octopus pot (takotsubo). [Previously unpublished ventriculogram provided by Dr. Ilan Wittstein and reproduced with permission.]

The illness is commonly attributed to very high levels of norepinephrine released from activated sympathetic nervous outflow to the heart (97) with severe stress, most commonly mental stress, although physical stressors also can be operative (1, 10). Although the cardiac sympathetic nerves may be pivotal, the distribution of the disordered myocardial contractility in the left ventricle, most developed at the apex, does not parallel the density of the cardiac sympathetic nerves (which shows a descending nerve density gradient from cardiac base to apex), contrary to expectations if the condition is neurally mediated.

My own studies on acute stressor responses in the heart do suggest another possible neural mechanism, involving the sympathetic neurotransmitter, NPY. NPY is released from sympathetic nerves at very high rates of nerve firing as an ancillary neurotransmitter. The concentration of NPY in the left ventricle, contained within sympathetic nerves, does match the pattern of ventricular dysfunction in takotsubo cardiomyopathy, increasing from base to apex. My own studies demonstrate NPY release from the sympathetic nerves of the heart in...
patients with panic disorder during the high levels of sympathetic activation present during panic attacks (31).

NPY has been shown to have a vasoconstrictor action in the heart, so very high rates of release from sympathetic nerves might underlie the development of cardiomyopathy by causing a pathological reduction in myocardial blood flow. Takotsubo cardiomyopathy would thus represent a form of ischemic stunning. Unlike catecholamines, NPY is not directly arrhythmogenic, perhaps relevant to the scarcity of lethal arrhythmias in the disorder. To be emphasized, however, is the absence of takotsubo cardiomyopathy in patients with panic disorder. Perhaps the typically young age of panic disorder sufferers protects them, with takotsubo cardiomyopathy occurring primarily in women past middle age.

Depressive illness. Cardiology was slow to recognize that depressive illness is a cause of coronary heart disease, the defining observation being made by Nancy Frasure-Smith, a social scientist, while working in a department of cardiology (36). It is now clear that depressive illness is a primary cause of coronary heart disease and materially worsens the prognosis in those with existing heart disease. Earlier ideas that heart risk from depressive illness was primarily due to the loss of volution characteristic of the disorder leading to personal neglect and lack of adherence to preventive health measures are now discounted. The cardiology/psychiatry turf wars, once in evidence in this field, are now in the past. The American Heart Association recently advised the readership of Circulation (62a) that all patients with coronary heart disease should be evaluated for the presence of depressive illness.

A new development is the search for the elements of depressive illness pathophysiology that might convey the increased heart attack risk. Untreated patients with depression have long been known to exhibit chronic activation of the sympathetic nervous system. This sympathetic activation is now known to involve the sympathetic outflow to the heart (5a), with cardiac norepinephrine spillover values in some cases being elevated to a level seen in patients with cardiac failure. This could be very pertinent, given the demonstrable contribution of high cardiac sympathetic activation to poor prognosis in patients with cardiac failure (48). In the future there might, perhaps, be a place for β-adrenergic blockade or central sympathetic inhibition with imidazoline drugs for cardiac protection in treatment-resistant depressive illness, although this is speculative at present. Activation of platelets in depressive illness also has been described (72), perhaps predisposing to coronary thrombosis.

Essential hypertension. The general public has needed little persuasion that chronic mental stress can cause hypertension, sometimes even using the word “hypertensive” as a psychological descriptor for excitable or agitated behavior. Many personally relate to the “tense” in hypertension and perhaps may be too ready to attribute their elevated blood pressure to stress in their job or domestic life.

Epidemiological research, however, does provide increasingly strong support for the notion that behavioral and psychological factors may be important in the pathogenesis of essential hypertension. Of particular relevance in this regard are studies linking hypertension development to chronic mental stress in the workplace (13, 85, 99). The study by Chandola et al. (13) is unique in specifically linking workplace stress to the development of the metabolic syndrome.

Recent research by my group breaks with the epidemiological methodology of the past in searching for the presence of stress biomarkers in patients with essential hypertension (29). Parallels are noted with panic disorder, which provides an explicit clinical model of recurring stress responses (33). 1) There is clinical comorbidity; panic disorder prevalence is increased threefold in essential hypertension (17). 2) Plasma cortisol is elevated in both. 3) For both, adrenaline cotransmission and induction of the adrenaline-synthesizing enzyme phenylethanolamine N-methyltransferase is present in sympathetic nerves. Experimental studies in rats show both to be an explicit indicator of mental stress exposure. 4) Tissue nerve growth factor is increased in both conditions, with nerve growth factor being a stress reactant.

Given the propensity for litigation in the developed world, regrettably we might now perhaps have a new hypertension subcategory to accompany essential hypertension, secondary hypertension, and labile hypertension in the blood pressure lexicon: “medicolegal hypertension.”

No “statins” yet for psychogenic heart disease. The benefits in terms of heart attack prevention achieved by blood cholesterol lowering with statins far outstrip those seen with stress reduction and treatment of psychiatric illness, which to this point are negligible or nonexistent. Treatment of depressive illness has not been shown to reduce rates of first myocardial infarction or sudden death. The SADHART study (38) demonstrated safety of serotonin reuptake-blocking drugs used to treat patients with depressive illness present after myocardial infarction, but there was minimal reduction in reinfarction rates. A vagal blocking effect of selective serotonin reuptake inhibitors, evident in reduced heart rate variability and lowered arterial baroreflex sensitivity in treated patients with depressive illness, has been described (18) This might perhaps counterbalance, in terms of cardiac risk, the benefit gained from inducing a remission in the depressive illness.

The field is now at a crossroads, given the lack of clear evidence of benefit in terms of heart attack prevention from treatment of depressive illness. One view heard is that the pathophysiological mechanisms of cardiac risk in depressive illness need to be better delineated, and specifically targeted pharmacologically, beyond the treatment of the depressive illness itself. This idea is not fanciful, given that many patients with depressive illness fail to remit fully with psychiatric treatment.

EDITORIAL COMMENTS

Regionalization of Sympathetic Nervous Responses

An assumption underlying application of the early tests of the sympathetic nervous system used in clinical research, measures of urinary norepinephrine excretion and plasma norepinephrine concentration, was that the sympathetic nervous system acts in a global, undifferentiated fashion. This was in accord with the teaching of a pioneer of the field, Walter Cannon (12), exemplified in his “fight and flight” concept of sympathetic mass action. Subsequent research has demonstrated that responses in the sympathetic nervous system are often regionalized, with activation in one sympathetic outflow commonly being accompanied by no change, or a reduction, in others (26, 28, 79). The recent monograph of David Goldstein (41) comprehensively affirms this principle. Definitive inves-
tigation of the human sympathetic nervous system requires the study of regional sympathetic outflows, despite the technical difficulties encountered.

**β-Adrenergic Blockade in Heart Failure Patients**

The translation of knowledge of pathophysiology into better medical care for patients is an important goal for clinical scientists. For the sympathetic nervous system, the achievement of this transition, from mechanisms to medical management, is perhaps best exemplified in cardiac failure, where knowledge of the neural pathophysiology in the heart led to the introduction of β-adrenergic blockers, a lifesaving form of treatment.

**Antiarhythmic Antihypertensive Drugs**

Despite the general importance of the sympathetic nervous system in blood pressure regulation and the specific demonstration that the blood pressure elevation in essential hypertension is commonly initiated and sustained by sympathetic nervous activation, drugs antagonizing this system are currently underutilized in the care of patients with hypertension. Use of β-adrenergic blocking drugs is waning, given the propensity of this drug class to have adverse metabolic effects, including predisposition to diabetes development. The recent blood pressure lowering achieved with radiofrequency ablation of the renal sympathetic nerves in patients with otherwise uncontrollable hypertension (59, 82) affirms the importance of the sympathetic nervous system in hypertension pathogenesis and suggests a wider role for antiarhythmic antihypertensives, such as the imidazoline drug class (moxonidine, rilmenidine), which act within the CNS to inhibit central sympathetic outflow.

**Disorders of Postural Circulatory Control**

Medical disorders characterized by fainting while standing are common and disabling. Some are attributable to neural degenerative disease of the brain or sympathetic nerves. More commonly, particularly in younger people, the cause is one of a number of poorly delineated functional disorders of postural circulatory control. Medical management in the latter is commonly unsatisfactory and will remain a therapeutic “tilting at windmills” until better categorization of the neural circulatory pathophysiology, such as has been attempted here, provides substantiated, logical drug targets.

**Psychogenic Heart Disease**

Medical conservatism long delayed acceptance of the now proven proposition that mental stress and psychiatric illness are a cause of heart disease. Activation of the sympathetic outflow to the heart either episodically, in triggering of cardiac arrhythmias or the causation of takotsubo cardiomyopathy, or chronically, in depressive illness appears to be a common mediating mechanism, providing a potential therapeutic target for future breaking of this adverse mind-heart link.

**DISCLOSURES**

M. Esler has a consultancy with Ardian, Inc. (Palo Alto, CA).

**REFERENCES**


