What are Dysautonomias?

Dysautonomias are conditions where altered activity of the *"automatic" nervous system (the autonomic nervous system)* is harmful to health.

In Dysautonomias, What Goes Wrong?

Probably the most common type of *dysautonomia* is a condition where altered *autonomic nervous system* function worsens another disease process that happens to be going on at the same time. For instance, when a person shovels snow, the exercise and cold exposure while standing up activate the *sympathetic nervous system*, and this increases the blood pressure, pulse rate, and the force of the heartbeat, which are appropriate responses. More blood is delivered to the heart muscle, which uses up oxygen because of the increased work of the heart. But if the person has severe *coronary artery disease*, where the blood vessels that are supposed to deliver blood to the heart muscle are narrowed, the blood supply does not increase to meet the increased demand for oxygen. This imbalance can lead to a heart attack or fatal abnormal heart rhythm. In other words, in this situation, the increased sympathetic nervous system outflow would be appropriate, but the person ends up suffering anyway, because of the worsening of an independent disease.

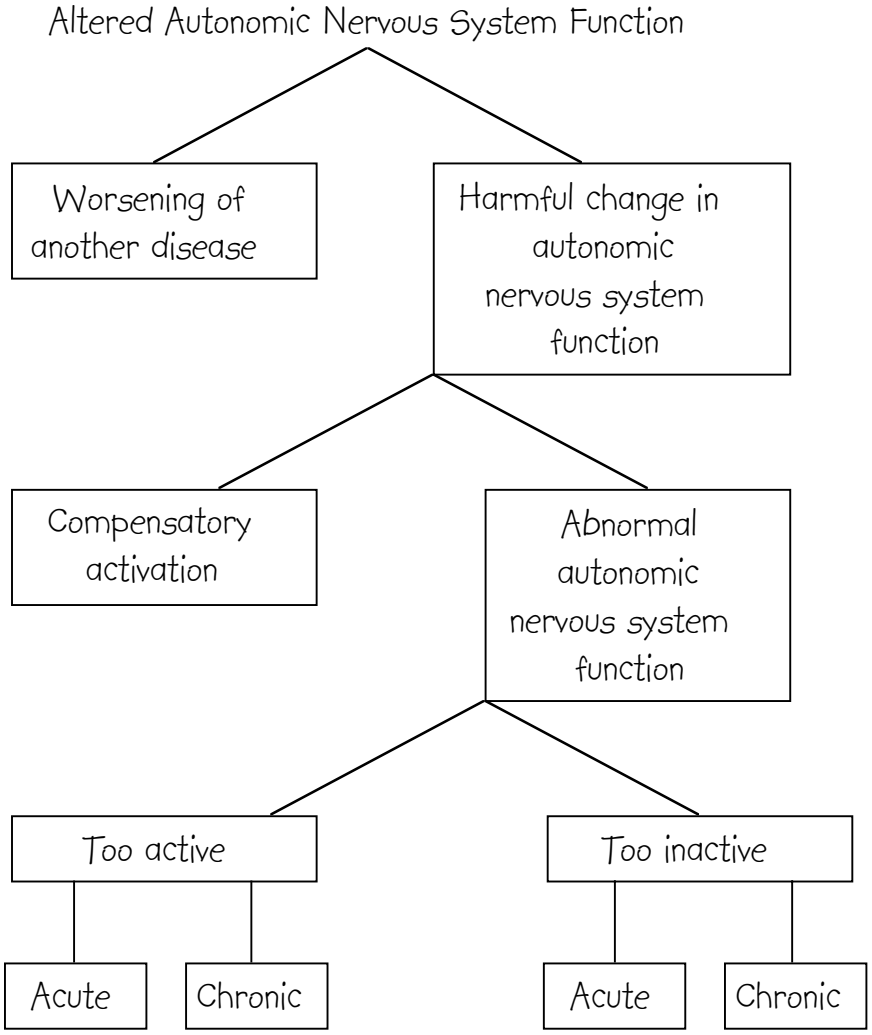
In other forms of *dysautonomia*, the problem is from abnormal function of the *autonomic nervous system* itself. This is the form of *dysautonomia* that most of the rest of this book is about.

Altered "automatic" nervous system function can worsen another disease or can itself harm health. In this book, "dysautonomias" refer to disorders of the autonomic nervous system itself.

For a variety of reasons, we know much more about what goes wrong with the *sympathetic nervous system* than with other parts of the *autonomic nervous system* in *dysautonomias*.

In general, there are two ways *dysautonomias* can result from abnormal function of the *sympathetic nervous system*. The first is when the system is activated to take over when another system fails. We call this compensatory activation. The second is when there is a primary abnormality of the system.

Finally, there are two general ways the function of the *sympathetic nervous system* can be abnormal. The first is by underactivity of the system, and the second is overactivity of the system. Both underactivity and overactivity of the *sympathetic nervous system* can be persistent and long-term or can be occasional and short-term in other words, chronic or episodic.



There are four types of dysautonomia, depending on whether there is too much or too little activity and whether the condition is new or has been going on a long time.

The "Mind-Body" Issue

It is worthwhile to discuss here the issue of the "mind versus body" as a primary cause of disease, because *dysautonomias* are, possibly more than any other ailments, mind-body disorders.

Dysautonomias are mind-body disorders.

This is a difficult subject for both doctors and patients. The problem is the old notion that the body and mind are separate and distinct in a person, and so diseases must be either physical or mental. If the disorder were physical, it would be "real," something imposed on the individual, while if it were mental, and "in your head," it would not be real, but something created in and by the individual.

Mind → Thoughts → Mental Illness

Body → Imposed Challenges → Physical Illness

Traditional separation of mental from physical illness.

Distinctions between the "body" and the "mind," the physical and mental, problems imposed on the individual and those in the mind of the individual, are unhelpful in trying to understand dysautonomias.

These notions date from the teachings of the Renaissance philosopher, Descartes. They are outdated by now and also inappropriate and unhelpful in trying to understand disorders of the *autonomic nervous system.*

Here is why. Remember in the first chapter you learned about the "inner world" and the "outer world"? The mind deals with both worlds, simultaneously, continuously, and dynamically in life. Conversely, both worlds affect the mind, and each individual filters and colors perceptions of the inner and outer world. For instance, there is no such thing as a person exercising without "central command," to tense and relax specific muscles. At the same time, and as part of the same process, the brain automatically directs changes in blood flow to the muscles. The exercising muscle and changes in blood flow lead to information—feedback—to the brain about how things are going both outside and inside the body.

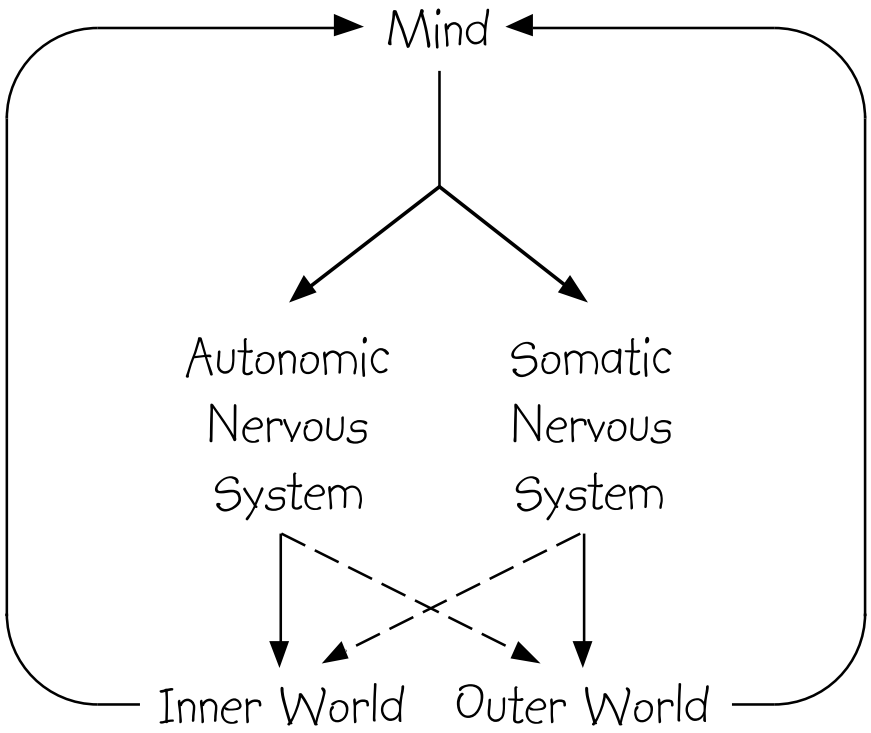
The autonomic nervous system operates at the border of the mind and body.

Now here is the key: The *autonomic nervous system* operates exactly at the border of the mind and body. The brain uses and depends on the *autonomic nervous system* for the internal adjustments that accompany every motion a person performs and every emotion a person feels.

You already know this, if you think about it. When you jog, for instance, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, and you move more air. These are automatic features of the experience of exercising. Can you imagine exercising and not noticing these things?

It's also true that virtually every emotion a person feels includes changes in the same body functions. For instance, when you are enraged, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, and you move more air.

From the point of view of the bodily changes, it would matter little whether these changes resulted from the physical experience of exercise or the mental experience of rage. Both situations involve alterations in the activity of components of the *autonomic nervous system.* Both



A systems approach to the mind-body issue.

situations involve changes in the inner and outer worlds. And if your *autonomic nervous system* were to malfunction, your reactions to **either** situation would not be regulated correctly, in either situation you could feel sick, look sick, and *be* sick!

A "systems" approach helps to understand *dysautonomias.* According to the systems approach, the mind simultaneously directs changes in the *somatic nervous system* and the *autonomic nervous system,* based

on perceptions about what is going on in the inner world and the outer world.

Note that the *autonomic nervous system* affects both the inner world and outer worlds. For instance, if a person looked pale, because the blood quite literally had drained from the face, and was sweaty, trembling, and mumbling incoherently, other people would likely react to these signs of distress and ask, “Are you OK?”And it is well known that strong emotions, probably via *adrenaline* release, can energize an individual. In fact, one of the entries under weightlifting in the Guiness Book of Records referred to a 123-pound mother who summoned the strength to lift the front end of a 3,600-pound car after a jack had collapsed and the car had fallen on her child!

Analogously, the *somatic nervous system* can affect the inner world. For instance, you can voluntarily increase your blood pressure any time you want, by clenching a tight fist, or dunking your hand in cold water.

How would a systems approach help to understand a *dysautonomia?* A malfunction at almost any part of the system could lead to an alteration in activity of the *autonomic nervous system.* For instance, if there were no feedback to the brain about the state of the blood pressure (part of the inner world), then there would be an inability to keep the blood pressure within bounds, by changing the activity of the *autonomic nervous system.* If there were no feedback about the extent of physical exercise, there would also be an inability to adjust the blood

pressure and blood flows appropriately. Of course, if there were a failure of the *autonomic nervous system* itself, this would also interfere with regulation of the inner world, but there would also be difficulty in dealing with the outer world, manifested by problems like exercise intolerance or an inability to tolerate standing for a prolonged period *(orthostatic intolerance).* Finally, if the person had a psychiatric disorder such as panic/anxiety, then the inappropriate emotional experience of fear would be linked to both *autonomic nervous system* and *somatic nervous system* changes.

A clinician's ability to treat a *dysautonomia* successfully would also benefit from a systems approach. Treatments at any of several steps might help, but the best place in the system to insert a treatment would be the step closest to where the problem is.

When in Life do Dysautonomias Occur?

Different types of *dysautonomia* occur in different stages of life.

Dysautonomias can occur at any age.

In infants and children, *dysautonomia* often reflects a genetic change, called a *mutation*. A mutation is like a "typo" in the genetic encyclopedia.

One type of mutation that runs in the family of people of east European Jewish extraction causes *familial dysautonomia*. Another *mutation* that produces *dysautonomias* in children causes a type of phenylketonuria (PKU). Another causes "kinky hair disease" (Menkes disease). In general, *dysautonomias* from genetic *mutations* are rare. In adults, *dysautonomia*

Infancy/Childhood

Sensory and Autonomic Neuropathy (SAN)
Familial Dysautonomia (a form of SAN)
Menkes Disease

Childhood/Adulthood

Postural Tachycardia Syndrome (POTS)
Neurocardiogenic Syncope (NCS)
Hypernoradrenergic Hypertension
Autoimmune Autonomic Failure
Acute Baroreflex Failure

Adulthood/Elderly

Diabetic Autonomic Neuropathy
Chemotherapy
Parkinson's Disease
Amyloidosis
Multiple Myeloma
Multiple System Atrophy (MSA)
Shy-Drager Syndrome (a form of MSA)
Pure Autonomic Failure (PAF)

Different forms of dysautonomia happen at different ages. Here are some examples.

usually reflects a functional change in a generally intact *autonomic nervous system*.

Examples are *neurocardiogenic syncope* (where the person has frequent episodes of fainting or near-fainting), *postural tachycardia syndrome* (where the person cannot tolerate standing up for long periods and has a rapid pulse rate during standing), and *hypernoradrenergic hypertension* (where overactivity of the *sympathetic nervous system* causes a form of high blood pressure). Less commonly, there is a loss of nerve terminals, such as caused by a toxic substance, viral infection, or the body attacking itself (*autoimmune autonomic failure*). Rarely, *dysautonomia* in adults reflects a genetic *mutation*, the one-in-a-million "typo" in the genetic encyclopedia, or a *polymorphism*, which is genetic change that is more common than a *mutation.*

In the elderly, *dysautonomia* usually reflects a degeneration of the *autonomic nervous system*, often in assocation with other evidence of degeneration of the brain. Examples are *multiple system atrophy* and *Parkinson's disease.*

How Are Dysautonomias Classified?

Since *dysautonomias* can be somewhat mysterious and controversial, doctors can disagree about the diagnostic classification of *dysautonomias*. In this section we follow the diagram about types of dysautonomia from a few pages ago.

Doctors can disagree about how to classify dysautonomias.

As you read about the *dysautonomias,* keep in mind that the particular labels that are given for many of these conditions are "best guesses;" many labels refer to essentially the same set of symptoms; even with the same label, different people can have very different symptoms; and actual mechanisms for many of these conditions are not well understood. Further research will lead to discoveries about the causes of these conditions, and new, definitive names for the conditions.

The primary concern for the patient and doctor should be symptom management, which will provide relief and better quality of life.

Changes in *autonomic nervous system* function can adversely affect health by **worsening another disease**. One example of this is the activation of the **sympathetic nervous system** during exercise in the cold, such as during shoveling snow. Both cold exposure and exercise increase activity of the *sympathetic nervous system*. Under normal circumstances this helps the person, by preserving and generating body heat and by delivering more blood to the muscles. The blood pressure and pulse rate increase, the work of the heart increases, and the blood flow to the heart muscle by the *coronary arteries* normally increases. But if the person has severe *coronary artery disease,* where the *coronary arteries* feeding the heart are narrowed, then when the work of the heart increases, due to activation of the *sympathetic nervous system,* the blood flow in the *coronary arteries* does not increase. This imbalance between the limited delivery of oxygen by the blood and the increased demand for oxygen can produce chest pain or pressure, heart attacks, or fatal abnormalities in heart rhythm. In other words, what would in other situations be a normal, helpful increase in *sympathetic nervous system* activity ends up worsening the health of the patient, in this case by turning "silent" *coronary artery disease* into a killer.

Changes in *autonomic nervous system* function can also be harmful, when activity of the system changes to **compensate** for abnormal functioning of a different body system. For instance, in *heart failure,* the heart fails to deliver an appropriate amount of blood to body organs. As compensation to improve the pump function of the heart, the *sympathetic nervous system* is activated. At the same time that this can improve the pump function of the heart, the activation of the *sympathetic nervous system* also increases the risk of fatal abnormal heart rhythms, increases the work of the heart, and promotes overgrowth of heart muscle, which can stiffen the heart walls and worsen the heart failure.

When doctors think about *dysautonomias,* they usually don't think about altered function of the *autonomic nervous system* worsening another disease, or about harmful effects of *compensatory activation* when another system fails. Instead, doctors think about abnormal function of the *autonomic nervous system* itself.

In general, there are four types of abnormal function of the *autonomic nervous system.* There may be acute overactivity, chronic overactivity, acute underactivity, and chronic underactivity. The next chapters describe these disorders.

In What Conditions is the Autonomic Nervous System Underactive?

Different parts of the autonomic nervous system are underactive in different disorders.

When the *parasympathetic nervous system* is underactive, the person has constipation, retention of urine in the bladder, a tendency to fast pulse rate, decreased salivation, and in men *impotence.* Several drugs can cause this combination of problems, but sometimes they result from failure of some part of the *parasympathetic nervous system.* Whether the problem is in the brain, in the nerve traffic from the brain, in the *ganglia* that act like transfer stations on the nervous system highway, in the nerve terminals preventing release of the chemical messenger, *acetylcholine,* or in the *receptors* for *acetylcholine* in the tissue, the effects in terms of the way the patient feels and looks are about the

Parasympathetic nervous system underactivity produces constipation, urinary problems, fast pulse rate, decreased spit, or (in men) an inability to have an erection.

same. In other words, many different mechanisms can result in the same symptoms.

The *parasympathetic nervous system* is underactive in several types of *dysautonomia,* including *Parkinson's disease* with *autonomic failure, pure autonomic failure,* and *multiple system atrophy.* All these types of *dysautonomia* also feature underactivity of the *sympathetic nervous system* too, and they are discussed later in separate sections. Parasympathetic functions tend to decrease also with normal aging.

When the *sympathetic nervous system* is underactive, the person has a fall in blood pressure if the patient stands up, which is called *orthostatic hypotension.* Sympathetic failure produces a tendency to slow pulse rate and in men inability to ejaculate. Several drugs can cause this combination of problems, but sometimes they result from failure of some part of the *sympathetic nervous system.*

A fall in blood pressure when the patient stands (orthostatic hypotension) is an important sign of failure of the sympathetic nervous system.

As for underactivity of the *parasympathetic nervous system*, whether the problem is in the brain, in the nerve traffic from the brain, in the *ganglia*, in the nerve terminals preventing release of the chemical messenger, *norepinephrine*, or in the *receptors* for *norepinephrine* in the tissue, the effects in terms of the way the patient feels and looks are about the same.

Sweating and blood pressure are "automatic" functions controlled by different chemicals.

Since *acetylcholine* is the main chemical messenger used by the *sympathetic nervous system* for sweating, while *norepinephrine* is the main chemical messenger used by the *sympathetic nerve system* to tighten blood vessels and maintain blood pressure during standing, a patient with a specific problem in the production, release, or *receptors* for *norepinephrine* could have *orthostatic hypotension* and yet sweat normally.

The *sympathetic nervous system* is underactive in several types of *dysautonomia,* including *Parkinson's disease with autonomic failure, pure autonomic failure, and*

multiple system atrophy. Acute *sympathetic failure* also appears to play a key role in fainting.

When the *adrenomedullary hormonal system* is underactive, the effects on the body are much more subtle than when the *parasympathetic nervous system* or the *sympathetic nervous system* is underactive. This is probably because the *adrenomedullary hormonal system* is activated in relatively unusual emergency situations. When you are at rest, your *adrenal glands* release very little *epinephrine* into the bloodstream.

Epinephrine (adrenaline) is one of the body's main hormones for regulating blood levels of *glucose*, one of the body's main fuels. Failure of the *adrenomedullary hormonal system* can cause a tendency to low glucose levels, a condition called *hypoglycemia.* This can be a major problem in patients who have *diabetes* and take injections of *insulin*, because failure of the *adrenomedullary hormonal system* in these patients can result in susceptibility to severe *hypoglycemia* reactions to the *insulin.*

Failure of the adrenomedullary hormonal system can cause a tendency to low glucose levels (hypoglycemia).

What is Orthostatic Hypotension?

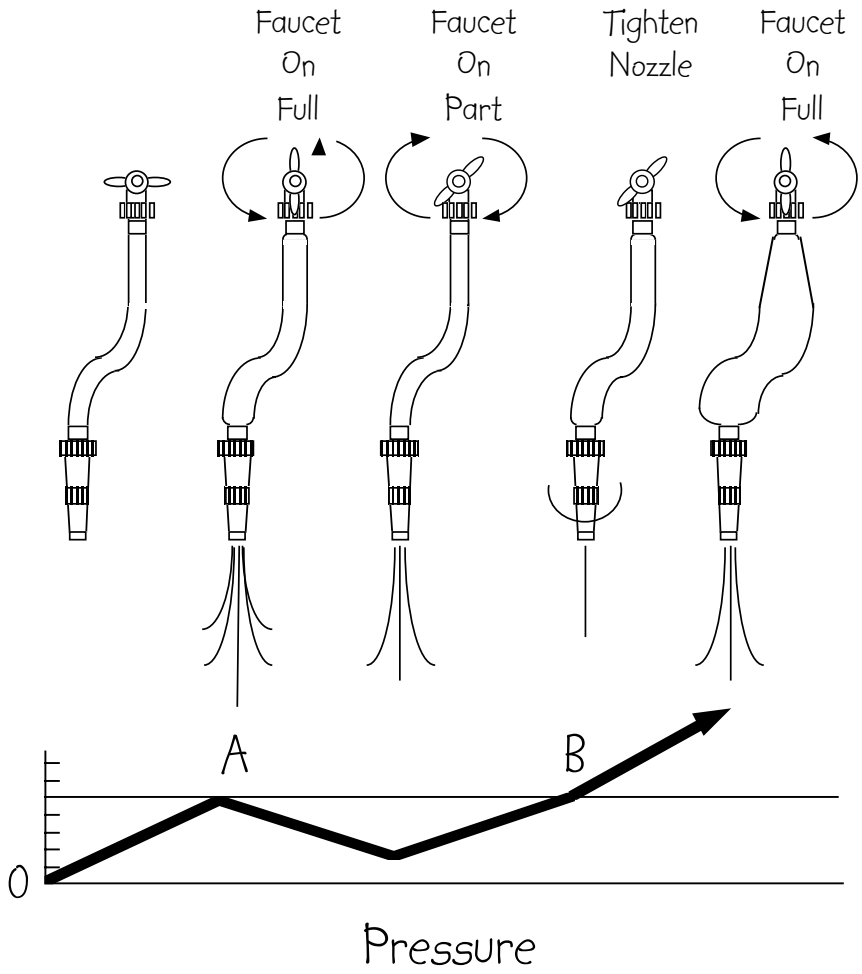
Normally, when you stand up, you don't notice much that is different. Nevertheless, there are quite a few automatic, largely unconscious, reflexive changes directed by the brain that are required for tolerating the act of simply standing up. When the reflexes fail, the patient can't tolerate simply standing up. If the blood pressure falls by more than 20 millimeters of mercury between lying flat and standing up, this is called orthostatic hypotension.

Inability to tolerate standing up, or *orthostatic intolerance,* is a symptom, a complaint about something abnormal a person notices that provides subjective evidence of a disease. A fall in blood pressure when a person stands up, or *orthostatic hypotension,* is a sign, something a doctor can observe or measure that provides objective evidence of a disease. Neither *orthostatic intolerance* nor *orthostatic hypotension* is a diagnosis, which is a decision about the cause of a specific case of disease.

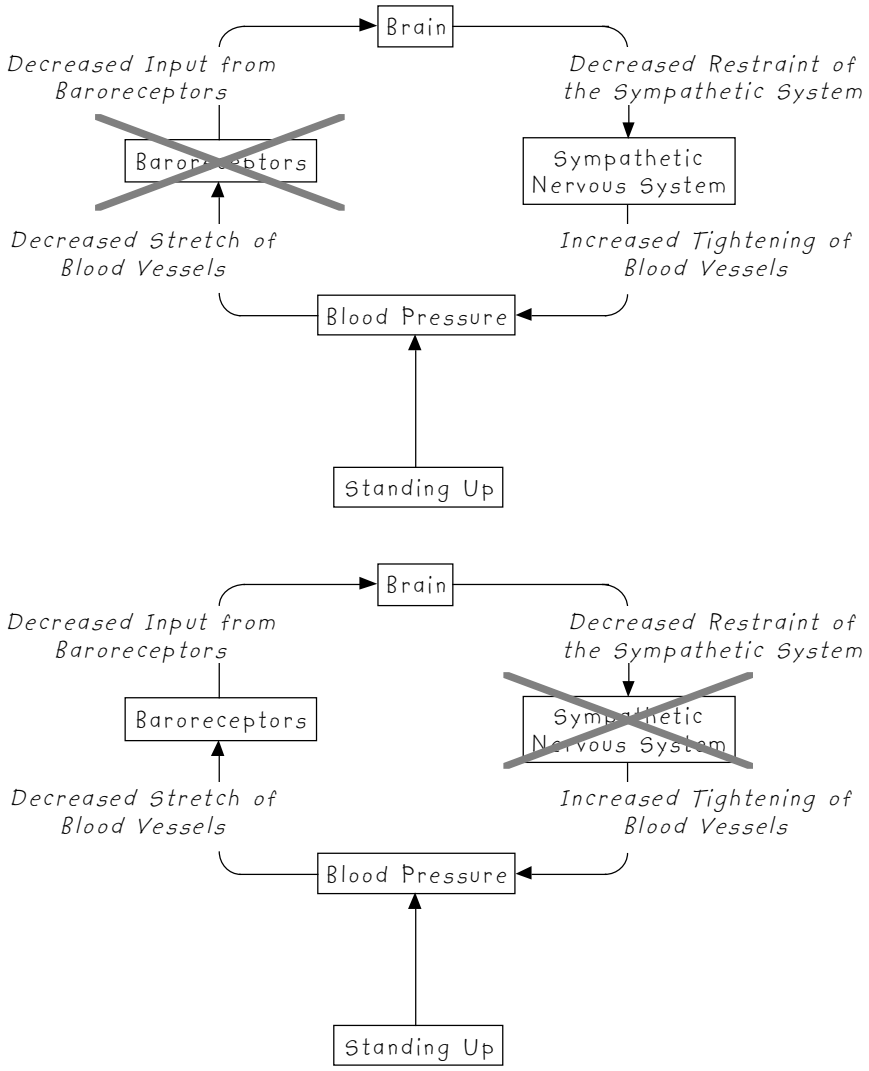
Orthostatic hypotension: a 20 point or larger fall in blood pressure when a person stands up from lying down.

When a person stands up, this sets into motion an important reflex called the *baroreflex.* The *baroreflex* helps to maintain the blood pressure. When a person stands up, the force of gravity tends to pool blood in the legs and lower abdomen. This decreases the return of blood to the heart in the veins. The heart ejects less blood. *Baroreceptors* are tiny distortion receptors in the walls of large vessels and in the heart muscle. When the heart ejects less blood, information changes in nerves traveling from the *baroreceptors* to the brain. The brain responds by directing an increase in the activity of the *sympathetic nervous system*. The *sympathetic nerves* release *norepinephrine*, and the *norepinephrine* activates *receptors* on cells in the blood vessel walls. This tightens the blood vessels, and so the total resistance to blood flow in the body increases. In other words, the *total peripheral resistance increases.* Even though the total amount of blood ejected by the heart per minute *(cardiac output)* has decreased, the average *blood pressure* normally is maintained, due to the increase in *total peripheral resistance.*

You might understand the *baroreflex* better by thinking about the water pressure in a garden hose. The pressure is determined by how much the faucet is turned on and how much the nozzle is tightened. If you turned down the faucet, the pressure in the hose would decrease, and less water would come out the nozzle. If you wanted to keep the pressure in the hose the same, you could tighten the nozzle.



There are two ways to control the pressure in a garden hose: the faucet and the nozzle. There are two ways to control blood pressure: cardiac output and total peripheral resistance.



The baroreflex and sympathetic nervous system must both work, for a person to tolerate standing up.

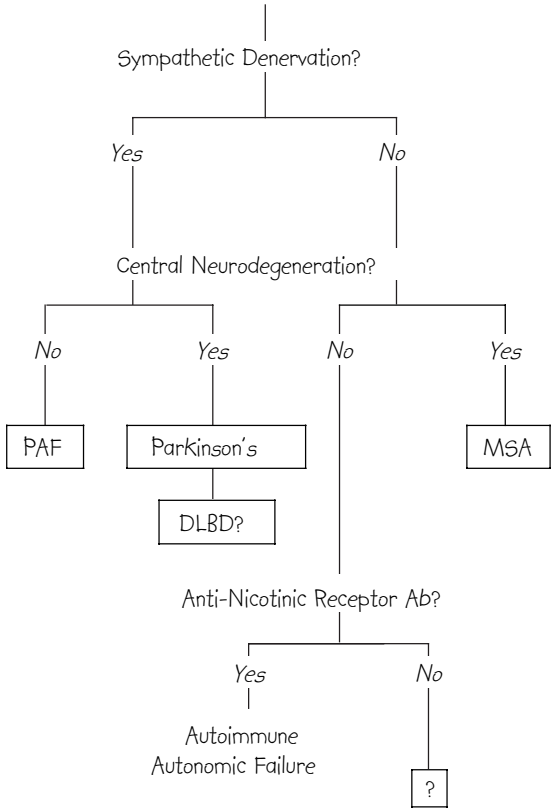
Baroreflexes control the amount of tightening of the blood vessels. When a person stands up, the blood vessels tighten reflexively, helping maintain the blood pressure, and the main system responsible for tightening the vascular nozzle is the *sympathetic nervous system.* This explains why failure of the *sympathetic nervous system* always causes *orthostatic hypotension.*

In sympathetic nervous system failure, the patient can't tighten the "nozzle."

Doctors may have different opinions about the amount of *orthostatic hypotension* that is clinically significant. Normally the systolic pressure falls slightly during standing up, because the heart is ejecting less blood, and normally the diastolic pressure does not fall at all, because of the reflexive constriction of blood vessels in the body as a whole. In general, if the *systolic blood pressure* (the peak pressure when the heart beats) decreases by more than 20 millimeters of mercury and the diastolic pressure decreases by more than 5 millimeters of mercury, then the patient has *orthostatic hypotension*.

Orthostatic hypotension is a key sign of *sympathetic neurocirculatory failure.* Any of several diseases can produce *orthostatic hypotension* from *sympathetic neurocirculatory failure.*

Sympathetic Neurocirculatory Failure



Sympathetic neurocirculatory failure has many potential causes.

These include *pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease, diffuse Lewy body disease (DLBD), and autoimmune autonomic*

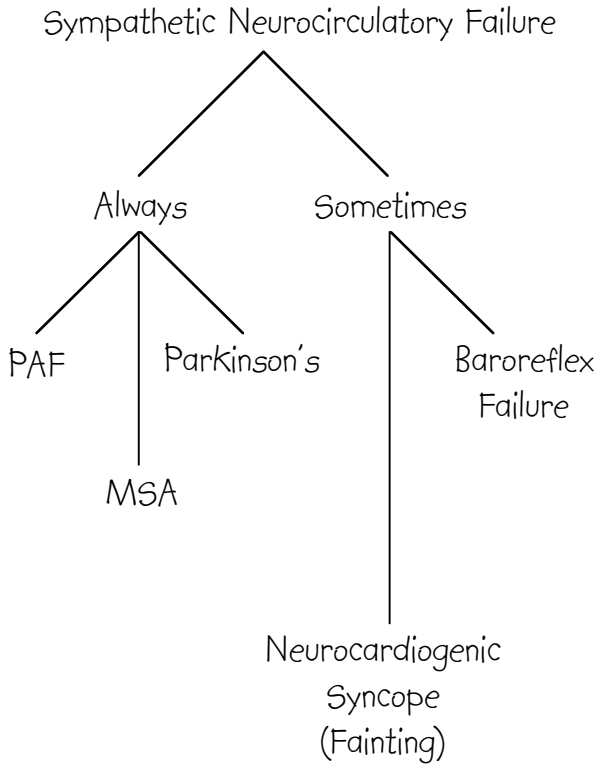
failure. In these diseases, orthostatic hypotension occurs persistently and consistently.

There are other disorders where the patients cannot tolerate prolonged standing, even though they do not have persistent, consistent *orthostatic hypotension.* These *orthostatic intolerance* syndromes are discussed later.

Remember that neither *orthostatic intolerance* nor *orthostatic hypotension* is a disease. One is a symptom (or set of symptoms) that a person has when standing. The other is a sign that a doctor can measure.

Many factors besides *sympathetic neurocirculatory failure* can cause *orthostatic hypotension.* Prolonged bed rest for virtually any reason can do this. Indeed, in the American space program, a study of normal volunteers in perfect health found that after prolonged bed rest with the head slightly down, these healthy people often developed *orthostatic hypotension.* It should not be surprising that elderly, bedridden patients also routinely have *orthostatic hypotension. Orthostatic hypotension* can also result from conditions that cause depletion of blood volume, such as heavy menstrual periods or gastrointestinal hemorrhage from a bleeding ulcer.

There are many causes of orthostatic hypotension, besides sympathetic nervous system failure.

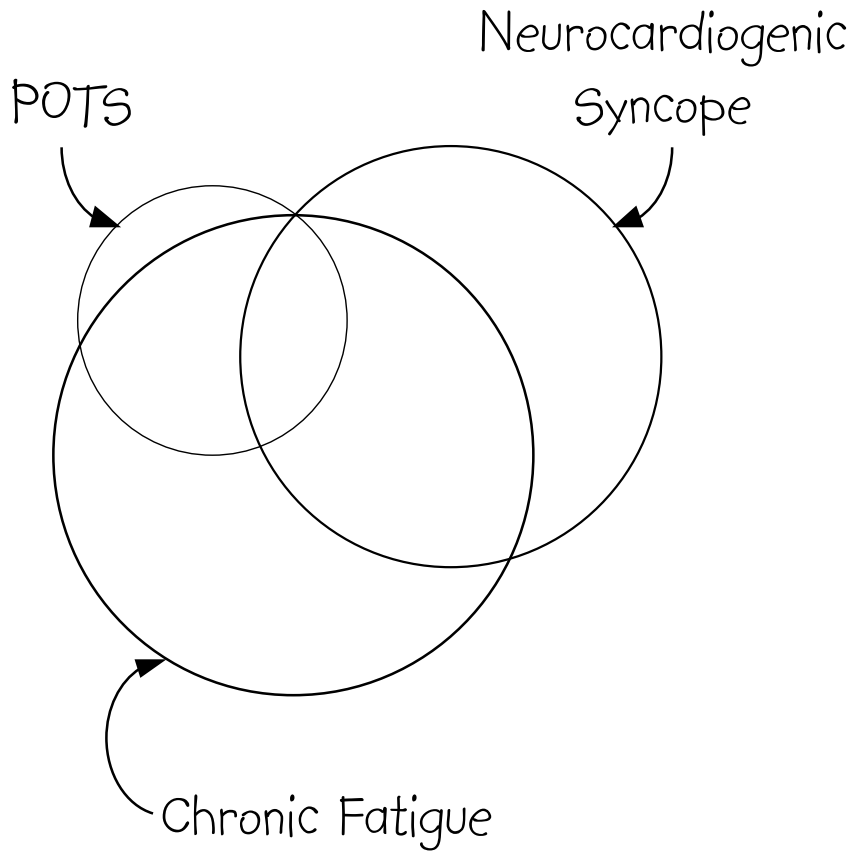


Failure of the sympathetic nervous system to regulate blood pressure occurs in both persistent diseases and occasional episodes.

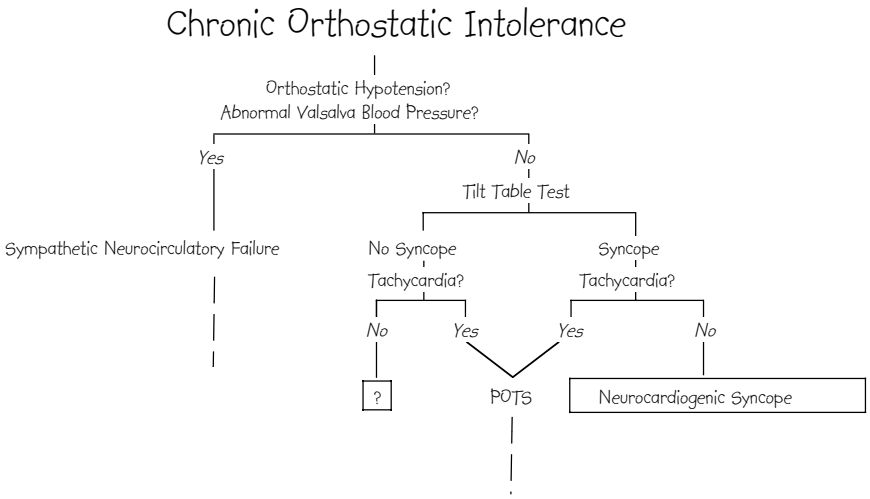
What is Orthostatic Intolerance?

A major main way *dysautonomias* cause problems is by producing *orthostatic intolerance.* Remember that orthostatic intolerance is based on **symptoms**, such as dizziness or lightheadedness while standing. *Orthostatic intolerance* is not a **sign**, because it isn't something an observer can measure objectively. And it isn't a **disease** (although there are many diseases that produce *orthostatic intolerance).* The fact that there are many possible causes of *orthostatic intolerance* poses a challenge to any doctor trying to come up with a diagnosis to explain *orthostatic intolerance* in a particular patient.

Patients with orthostatic intolerance can't tolerate prolonged standing.



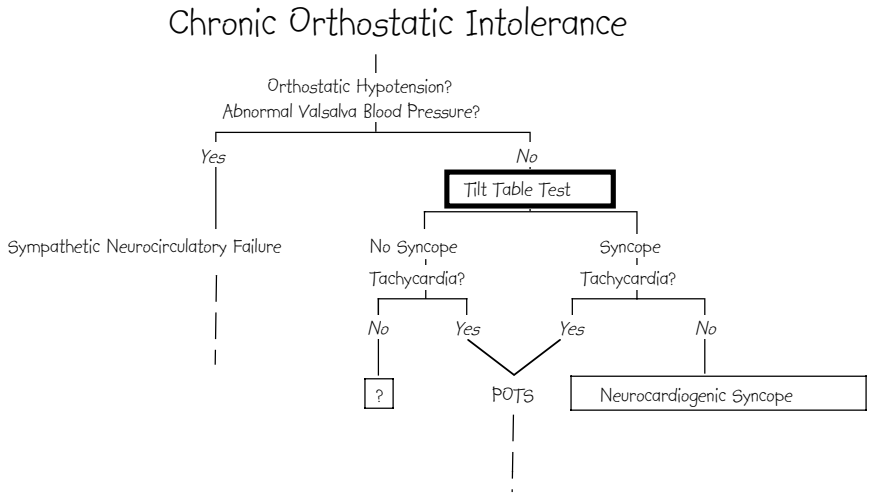
About 60% of patients with Chronic Fatigue Syndrome have Chronic Orthostatic Intolerance, with Postural Tachycardia Syndrome (POTS), Neurocardiogenic Syncope, or both.



One approach in the diagnosis of chronic orthostatic intolerance is based on whether the patient has a fall in blood pressure during standing (orthostatic hypotension).

Patients with *Chronic Fatigue Syndrome* often have *orthostatic intolerance.* The *orthostatic intolerance* can be associated with *postural tachycardia syndrome (POTS), neurocardiogenic syncope,* or both.

A starting point in identifying a cause of *orthostatic intolerance* is to determine whether the patient has failure of the *sympathetic nervous system* to regulate the heart and blood vessels correctly. We call this *sympathetic neurocirculatory failure*. In *dysautonomias* that produce



Doctors often do tilt table testing in patients who cannot tolerate standing (orthostatic intolerance) and do not have a fall in blood pressure during standing (orthostatic hypotension).

chronic sympathetic neurocirculatory failure, the patient always has a fall in blood pressure during standing, or *orthostatic hypotension*.

In other forms of *chronic orthostatic intolerance*, the person does not have *sympathetic neurocirculatory failure*, and the blood pressure does not fall consistently when the person stands up (although the person can have delayed *orthostatic hypotension* after many minutes of standing). Instead, the person feels dizzy or lightheaded

during standing, even while the blood pressure is maintained. *Orthostatic hypotension* can produce *orthostatic intolerance,* but *orthostatic intolerance* can occur without *orthostatic hypotension.*

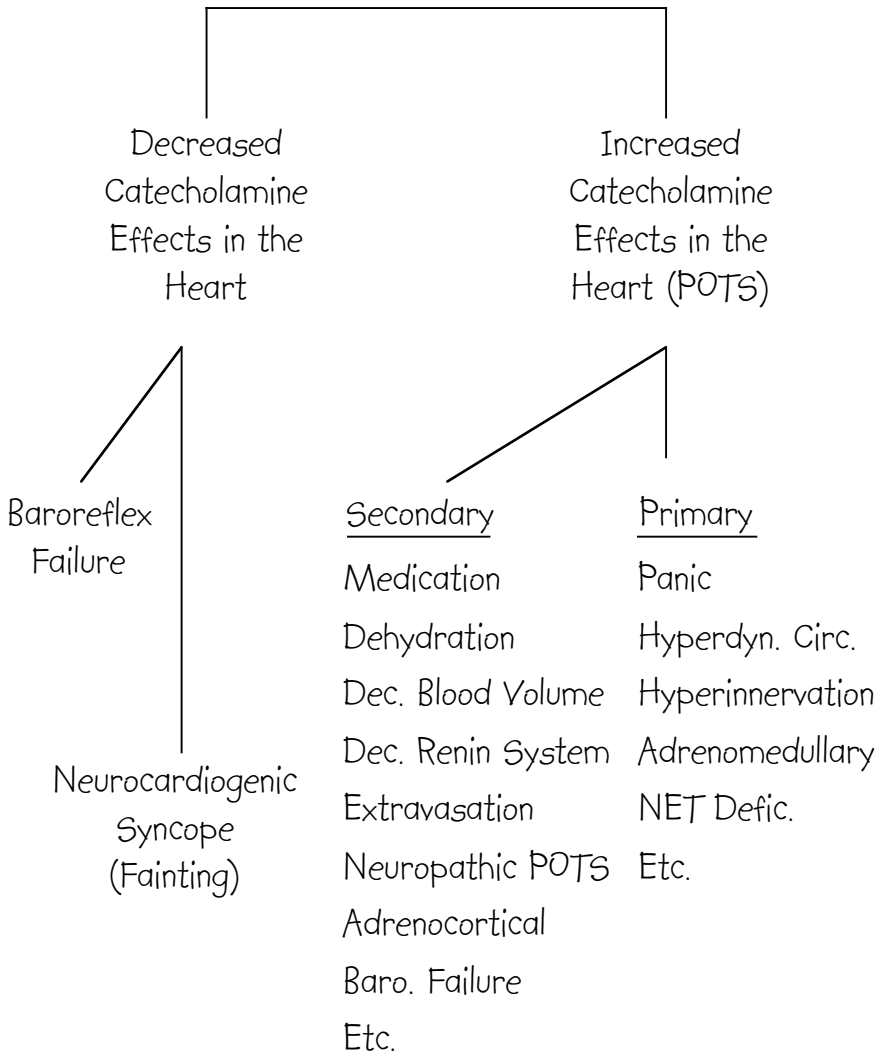
In the evaluation of a patient with *chronic orthostatic intolerance,* where the patient does not have evidence of *sympathetic neurocirculatory failure,* doctors often prescribe a *tilt table test.* The chapter about testing for *dysautonomias* discusses the *tilt table test.* In general, there are two types of positive *tilt table test* result. If the patient has an excessive, progressively more severe increase in pulse rate during the tilting, then this would be consistent with *postural tachycardia syndrome,* or *POTS.* If the patient has a decrease in the level of consciousness and finally loses consciousness *(syncope),* then this would be consistent with *neurocardiogenic syncope.* The loss of consciousness is virtually always associated with a fall in blood pressure, or *neurally mediated hypotension.* A tilt table test can also yield results consistent with both *POTS* and *neurocardiogenic syncope,* such as when the patient has a large increase in pulse rate, followed by a sudden fall in pulse rate back to normal, *neurally mediated hypotension,* and *syncope.*

Once a diagnosis of *POTS* is made, the workup may continue, to determine if the rapid pulse is part of a primary problem or is part of a compensation. The section about *POTS* discusses this workup.

In patients with *neurocardiogenic syncope,* the *sympathetic nervous system* can fail to work correctly only once in a while, in episodes, and in these episodes a person can feel faint or actually lose consciousness. A common form of *dysautonomia* where the *sympathetic nervous system* fails episodically is in *fainting,* which also has been called *neurally mediated syncope, neurocardiogenic syncope,* or the *common faint.* It is important to recognize that between episodes of fainting, patients with repeated episodes of *neurocardiogenic syncope* often do not feel well. In fact, they can complain of the same non-specific symptoms that patients with *POTS* describe, such as fatigue, heat intolerance, headache, exercise intolerance, and *orthostatic intolerance.*

The sympathetic nervous system fails when people faint.

Much less commonly, *orthostatic intolerance* reflects failure of the *baroreflex*. In this situation, the *sympathetic nervous system* is not activated appropriately in response to a decrease in blood pressure or in response to a decrease in *venous return* to the heart. Seemingly paradoxically, *baroreflex failure* does not necessarily cause *orthostatic hypotension,* but it does always cause large swings in blood pressure, both high and low, because of the inability of the *baroreflex* to keep the blood pressure within limits.



Orthostatic intolerance can be associated with increased or decreased effects of adrenaline-like chemicals in the heart.

Pure Autonomic Failure

This and the following sections describe several specific *dysautonomias.* The description is not meant to be exhaustive, and individual patients can have symptoms or signs that overlap.

Pure Autonomic Failure (PAF)

- *Mid-aged or elderly of either sex and any race*
- *Chronic, persistent fall in blood pressure during standing up*
- *No signs of brain disease*
- *Not inherited or infectious*
- *Can go one for many years*

Pure autonomic failure (PAF) features persistent falls in blood pressure when the patient stands—orthostatic hypotension—in the absence of signs of central nervous system disease and in the absence of other known causes of orthostatic hypotension. The *orthostatic hypotension* results from *sympathetic neurocirculatory failure.*

Pure autonomic failure, while chronic and causing disability, is not thought to be lethal.

Patients report progressively worsening dizziness standing up or after a large meal. Often they have decreased sweating. Because of severe *orthostatic hypotension, pure autonomic failure* patients often learn to sit or stand with their legs twisted pretzel-like, since this decreases pooling of blood in the legs. In men, impotence can be an early symptom.

In *patients with pure autonomic failure, blood pressure* responses to the *Valsalva maneuver* show the abnormal pattern that indicates *sympathetic neurocirculatory failure.* The *Valsalva maneuver* is discussed in the chapter about tests for *dysautonomias.*

The *sympathetic neurocirculatory failure* and *orthostatic hypotension* in pure autonomic failure typically result from loss of *sympathetic nerve terminals.*

Drug tests can confirm a diagnosis of *pure autonomic failure*. Because of the loss of *sympathetic nerve terminals,* drugs that release *norepinephrine* from *sympathetic nerves,* such as *yohimbine, amphetamine,* and *ephedrine,* produce relatively small increases in *blood pressure.* In contrast, drugs that directly stimulate *norepinephrine* receptors, such as *midodrine* and *phenylephrine* (Neo-Synephrine™) constrict blood vessels and increase *blood pressure*.

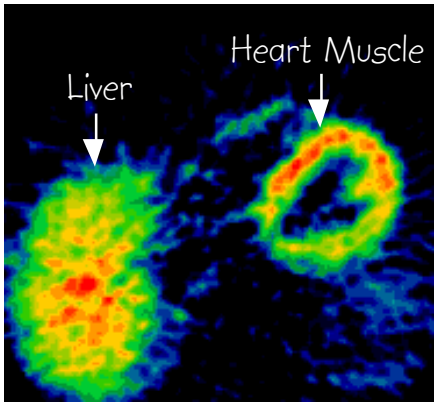
Because of the phenomenon of *"denervation supersensitivity,"* where *receptors* for *norepinephrine* increase and other adaptive processes probably occur that exaggerate constriction of blood vessels, patients with *pure autonomic failure* can have surprisingly large increases in blood pressure in response to the receptor-stimulating drugs.

As a result of loss of sympathetic nerve terminals, plasma *norepinephrine* levels typically are low in *PAF,* even with the patient lying down, and the levels fail to increase when the patient stands. In response to the above drugs, *plasma norepinephrine levels* fail to change as much as expected.

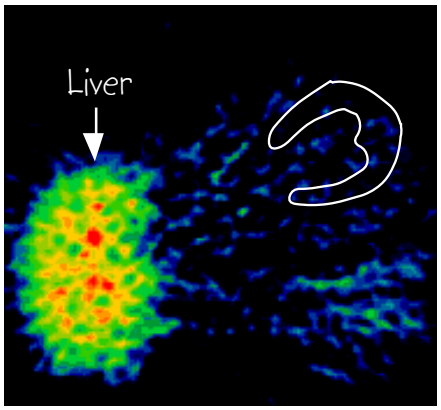
Another way to identify *PAF* is from *sympathetic neuroimaging.* In this type of test, the patient receives an injection of a radioactive drug that gets taken up by *sympathetic nerve terminals.* The *sympathetic nerves* in organs such as the heart become radioactive, and the nerves can be visualized by scans that detect where the radioactivity is, in a manner similar to commonly used clinical tests such as bone scans or brain scans. Since in *PAF* the *sympathetic nerve terminals* usually are absent in the organs, scanning after injection of one of these drugs fails to visualize the sympathetic *innervation. Sympathetic neuroimaging* tests such as *fluorodopamine PET* scanning of the chest usually produce remarkably graphic results in *PAF,* with a failure to visualize the heart walls at all.

No one knows what causes *pure autonomic failure.* It is not inherited, and no known environmental toxin causes it.

Treatment of *pure autonomic failure* is directed mainly at the *orthostatic hypotension,* which virtually always is severe and disabling. *Fludrocortisone,* a high salt diet, and *potassium* supplementation are the mainstays of treatment. Clinicians usually recommend elevation of the head of the bed. Body stockings may or may not help. The patient should not take large meals, because this may cause the *blood pressure* to decrease. Drugs that release *norepinephrine* from *sympathetic nerves,* such as *ephedrine, Ritalin*™, or *yohimbine,* may not work, because of the lack of nerve terminals, whereas drugs that artificially stimulate *receptors* for *norepinephrine,* such as *midodrine,* can be very effective.



Blood Flow
PET Scan



Sympathetic Nerve
PET Scan

Patients with Pure Autonomic Failure typically have a loss of sympathetic nerves in the heart muscle.

Multiple System Atrophy

Multiple system atrophy ("MSA") is a disease that involves progressive degeneration of multiple portions of the nervous system, including portions that regulate the *autonomic nervous system.* Several unconscious "vegetative" functions fail, such as digestion, urination, speech and swallowing mechanisms, and cardiovascular reflexes. Unlike *pure autonomic failure, MSA* is unfortunately a disease that is progressive and eventually lethal. On average, patients survive for about a half dozen years after the diagnosis is made. *MSA* differs from *multiple sclerosis,* which is characterized clinically by remissions and exacerbations and by relatively few changes in functions of the *autonomic nervous system.*

Multiple System Atrophy (MSA)

- *Mid-aged or elderly of either sex and any race*
- *Not inherited or infectious*
- *Chronic, persistent autonomic failure*
- *Signs of brain disease, such as slurred speech, rigidity, tremor, poor coordination*
- *Relentless progression over years*

No one knows what causes *MSA*. It is not inherited, and no known environmental toxin causes it. According to one view, *MSA* results from a form of *auto-immune* process, where the patient's immune system attacks and destroys particular brain cells.

MSA has different forms, which result in somewhat different symptoms and signs. In the *parkinsonian* form of *MSA (MSA_P)* the patient has symptoms and signs of *Parkinson's disease*, such as shakiness of the hands *(tremor)* that is most prominent at rest and decreases with intentional movements, muscular rigidity, and slow initiation of movement. Unlike in Parkinson's disease, these problems usually do not respond well to treatment with Sinemet™, the most commonly used drug for Parkinson's disease.

In the *cerebellar* form of *MSA (MSA_C)* the patient has symptoms and signs of failure of the *cerebellum*, which is a part of the brain that plays an important role in coordinated movements, coherent speech, balance, and accurate gait. If the patient has a *tremor*, it worsens with intentional movements. The typical patient also has slurred speech and a wide-based, "drunken sailor" type gait.

In the *mixed* form of *MSA (MSA_M)* the patient has a mixture of *parkinsonian* and *cerebellar* symptoms and signs.

MSA always involves one or more symptoms or signs of failure of the *autonomic nervous system*. Failure of the

parasympathetic nervous system produces *urinary retention* and *incontinence, constipation, erectile impotence,* and *decreased salivation.* Failure of the *sympathetic nervous system* produces a fall in *blood pressure* when the patient stands up *(orthostatic hypotension)* or after a meal *(post-prandial hypotension),* resulting in symptoms such as dizziness, weakness, or faintness upon standing or after eating.

MSA with failure of sympathetic reflexes *(sympathetic neurocirculatory failure)* is also known as the *Shy-Drager syndrome.* The most clear sign of *sympathetic neurocirculatory failure* is *orthostatic hypotension.*

MSA with a fall in blood pressure standing is also called the Shy-Drager syndrome.

Some investigators have equated *MSA* with the *Shy-Drager syndrome.* Others have considered *MSA* as an umbrella diagnosis that includes the *Shy-Drager syndrome* when *orthostatic hypotension* figures prominently in the clinical presentation but also includes forms where signs of *cerebellar atrophy* or of *Parkinson's disease* stand out. A recent proposal has recommended discarding using the *Shy-Drager syndrome* as a diagnosis.

Based on clinical findings and results of *autonomic function testing,* we have proposed a somewhat different classification scheme that distinguishes *MSA* with predominantly *parasympathetic* or other *brainstem*

degeneration from *MSA* with predominantly *sympathetic* degeneration, so that the *Shy-Drager syndrome* is synonymous with *MSA* and *sympathetic neurocirculatory failure.*

Symptoms and signs of *parasympathetic* degeneration include constipation and decreased urinary bladder tone, resulting in urinary incontinence, frequency, urgency, and the need for self-catheterization. Symptoms and signs of other brainstem degeneration include particular abnormalities in eye movements *("progressive supranuclear palsy"),* slurred speech, dyscoordinated swallowing, abnormal breathing, and repeated *aspiration,* where swallowed food goes into the airway. These problems can occur in patients with *MSA* who do not have *orthostatic hypotension* or other evidence of failure of the *sympathetic nervous system.*

In *MSA,* it is thought that the *autonomic failure* reflects loss of the ability to regulate *sympathetic* and *parasympathetic nerve traffic* to the *nerve terminals,* but the terminals themselves are intact. This appears to be a major difference between *MSA* and the usual form of *pure autonomic failure,* where the *autonomic failure* includes a loss of *sympathetic nerve terminals.* Because of the presence of intact *sympathetic nerve terminals,* patients with *MSA* have increases in blood pressure when they receive drugs such as *yohimbine* that release *norepinephrine* from sympathetic nerve terminals and have decreases in blood pressure when they receive drugs such as *trimethaphan* that decrease release of *norepinephrine* from *sympathetic nerve terminals.*

The fact that *trimethaphan*, which works by blocking transmission of autonomic nerve impulses in the *ganglia*, decreases blood pressure in patients with *MSA* means that in *MSA* the problem is not so much decreased *autonomic nerve traffic* as failure of the brain to regulate that traffic appropriately.

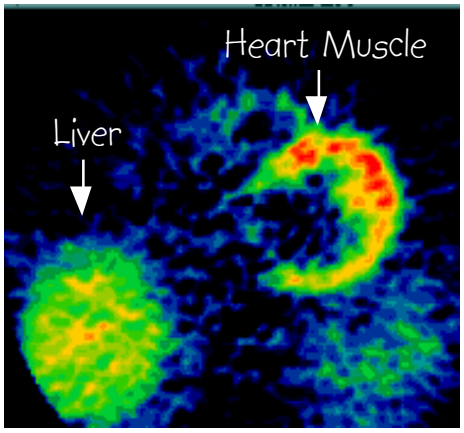
The widely used dietary supplement or herbal remedy, *ma huang*, is *ephedrine*, which releases *norepinephrine* from *sympathetic nerve terminals.* Since patients with *MSA and sympathetic neurocirculatory failure* have intact *sympathetic nerve terminals*, and they also have failure of the brain to regulate *sympathetic nerve traffic* appropriately via *baroreflexes*, taking *ma huang* can evoke a dangerous increase in blood pressure in these patients.

Patients with *MSA* appear to have approximately normal *sympathetic nerve traffic* to intact *sympathetic nerve terminals* when they are lying down, and so while they are lying down they usually have normal *plasma* levels *norepinephrine*, the chemical messenger of the *sympathetic nervous system.* The patients often have a failure to increase *sympathetic nerve traffic* when they stand up, and so they have a failure to increase plasma *norepinephrine* levels normally when they stand up. In contrast, patients with *pure autonomic failure*, who have a loss of *sympathetic nerve terminals*, usually have low plasma *norepinephrine* levels even when they are lying down.

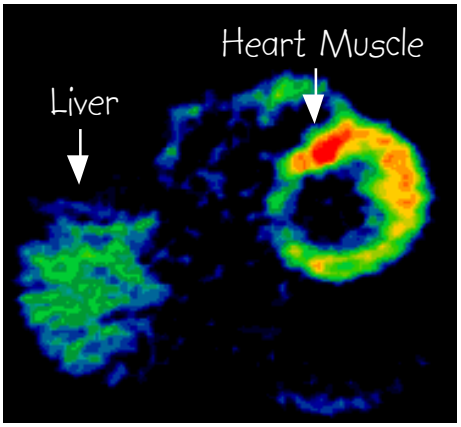
Another way to distinguish *MSA* from *pure autonomic failure* is from *sympathetic neuroimaging.* In this type of test, the patient receives an injection of a radioactive drug that gets taken up by *sympathetic nerve terminals.* The *sympathetic nerves* in organs such as the heart become radioactive, and the nerves can be visualized by scans that detect where the radioactivity is, in a manner similar to commonly used clinical tests such as bone scans or brain scans. Since in *MSA* the *sympathetic nerve terminals* are present in the organs, scanning after injection of one of these drugs visualizes the sympathetic *innervation.* In contrast, in *pure autonomic failure* (and in *Parkinson's disease,* discussed elsewhere), where the *sympathetic nerve terminals* typically are lost, *sympathetic neuroimaging* fails to visualize the sympathetic *innervation* of the heart.

The parkinsonian form of MSA can be difficult to distinguish from Parkinson's disease.

Distinguishing the *parkinsonian* form of *MSA* (MSA_P) from *Parkinson's disease* with *autonomic failure* can be a difficult diagnostic challenge. As mentioned above, one way to distinguish these diseases is from *sympathetic neuroimaging,* since patients with *MSA* have normal sympathetic *innervation* of the heart, and patients with



Blood Flow
PET Scan



Sympathetic Nerve
PET Scan (Normal)

MSA patients have normal sympathetic nerves in the heart muscle.

Parkinson's disease and orthostatic hypotension have a loss of sympathetic *innervation* of the heart.

Treatment of *MSA* is directed at the symptoms and signs, such as *orthostatic hypotension*, and does not prevent or delay the progressive deterioration of the nervous system.

Because of steadily worsening difficulty with coordination of speech and swallowing mechanisms, patients with MSA have a high risk of *aspiration*, aspiration pneumonia, bloodstream infection, or sudden death from stopped breathing.

Parkinson's Disease with Orthostatic Hypotension

Orthostatic hypotension, a fall in blood pressure when the patient stands up, occurs fairly commonly in *Parkinson's disease.* Neurologists have presumed that the *orthostatic hypotension* results from treatment with *levodopa,* or else the patient doesn't really have *Parkinson's disease* but has a different disease, such as *"striatonigral degeneration"* or *multiple system atrophy.*

Parkinson's Disease with Orthostatic Hypotension

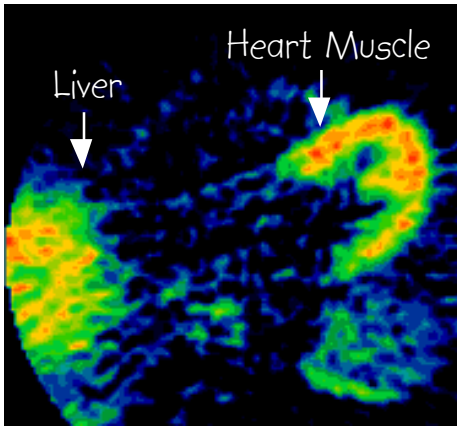
- *Elderly of either sex and any race*
- *Signs of Parkinson's disease, such as slow movements, rigidity, tremor*
- *Movement problem improves with Sinemet™ (DOPA+carbidopa)*
- *Chronic, persistent fall in blood pressure standing*
- *Can be inherited*
- *Slow progression over years*

Evidence is accumulating that all patients with *Parkinson's disease* and *orthostatic hypotension*—even patients off *levodopa* or never treated with *levodopa*—have failure of regulation of the heart and blood vessels by the *sympathetic nervous system.* In other words, in *Parkinson's disease, orthostatic hypotension* reflects *sympathetic neurocirculatory failure* and is therefore a form of *dysautonomia.*

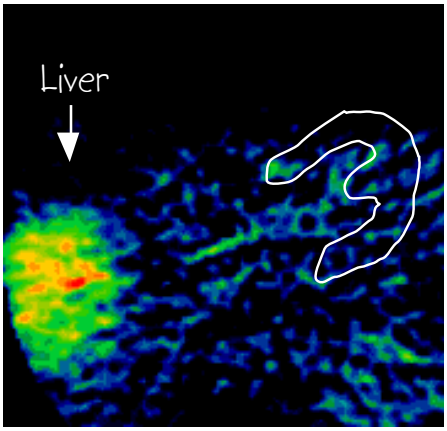
Patients with Parkinson's disease and a fall in blood pressure when they stand up have a form of dysautonomia.

In patients with *Parkinson's disease* and *orthostatic hypotension,* the *sympathetic neurocirculatory failure* appears to result from loss of *sympathetic nerve terminals* in the body as a whole. Because of the *sympathetic denervation,* there is a decreased amount of *norepinephrine* available for release in response to standing up, and failure to release an adequate amount of *norepinephrine* explains the *orthostatic hypotension* in *Parkinson's disease.*

Many patients with Parkinson's disease who do not have a fall in blood pressure when they stand up still have a loss of sympathetic nerves in the heart.



Blood Flow
PET Scan



Sympathetic Nerve
PET Scan

Patients with Parkinson's disease often have a loss of sympathetic nerves in the heart muscle.

Surprisingly, most patients with *Parkinson's disease* who do not have *orthostatic hypotension* nevertheless have

neuroimaging evidence for a loss of *sympathetic nerve supply* in the heart. *Parkinson's disease* therefore appears to be not only a disease of control of movement but also is *a dysautonomia*, because of the loss of *sympathetic nerve terminals.*

Pure autonomic failure also features *orthostatic hypotension* from loss of *sympathetic nerve terminals.* Some elderly patients with *pure autonomic failure* have subtle signs of *parkinsonism*, such as a mask-like facial expression and a type of stiffness of muscles. *Pure autonomic failure* can be difficult to distinguish from early or mild *Parkinson's disease* in these patients.

The long-term outlook in *Parkinson's disease* with *orthostatic hypotension* from *sympathetic neurocirculatory failure* seems about the same as in Parkinson's disease without *orthostatic hypotension.* The *orthostatic hypotension* does not appear to worsen with *levodopa* treatment, although the blood pressure both while lying down and when standing up can decrease.

The functional significance of loss of *sympathetic innervation* of the heart in *Parkinson's disease* remains unknown. One would presume that this would cause or contribute to an inability to tolerate exercise.

Treatments used for *Parkinson's disease* with *orthostatic hypotension* from *sympathetic neurocirculatory failure* include Florinef™ and a high salt diet, midodrine, frequent small meals and avoidance of large meals, and elevation of the head of the bed on blocks at night.

Treatments that depend on release of *norepinephrine* from *sympathetic nerve terminals*, such as *ephedrine, d-amphetamine*, *methylphenidate,* and *yohimbine,* may not work, because of the loss of the nerve terminals.

Patients with Parkinson's disease also often complain of constipation and urinary retention, urgency, and incontinence. These might reflect a form of failure of the parasympathetic nervous system; however, whether this is the case remains poorly understood. Failure of the parasympathetic nervous system supply to the heart appears to cause the constant pulse rate seen in most patients with Parkinson's disease and orthostatic hypotension; however, whether this reflects a loss of parasympathetic nerve terminals or a problem in regulating parasympathetic nerve traffic to intact terminals remains unknown.

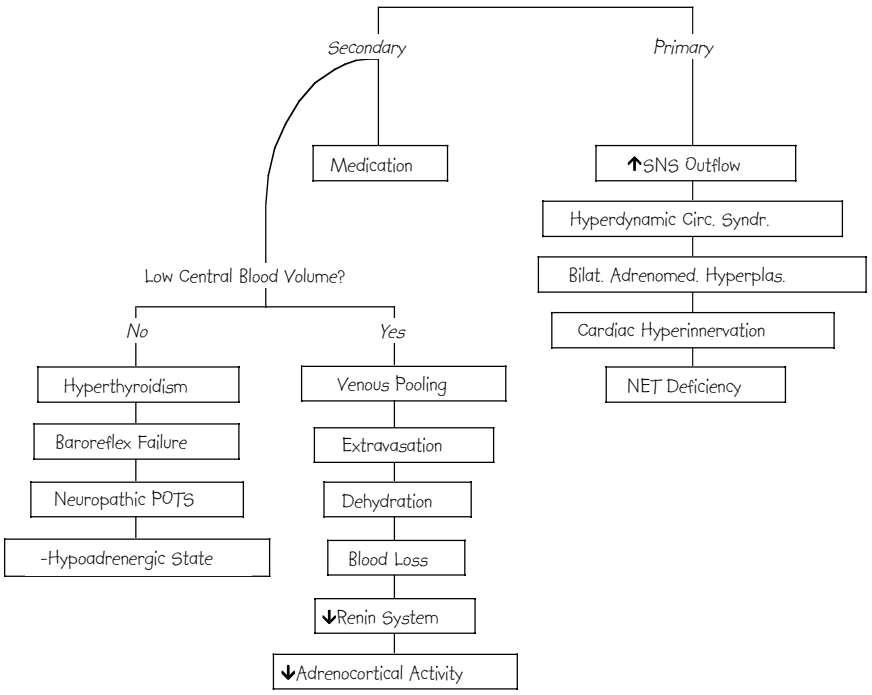
Postural Tachycardia Syndrome (POTS)

Patients with the *postural tachycardia syndrome (postural orthostatic tachycardia syndrome, POTS)* have an excessive increase in pulse rate during standing.

POTS patients have too rapid a pulse rate when they stand, and usually several other non-specific problems.

That being said, it should be pointed out at the beginning of this discussion that different research groups have different views about the classification of *dysautonomias*, and especially about *POTS* and *chronic orthostatic intolerance*. Just having a fast pulse rate while standing would not necessarily be harmful and cannot be a *syndrome*, which always involves more than a single symptom or sign.

POTS is associated with a variety of other symptoms that, when thought of individually, are not specific for any particular disease process. These include inability to tolerate prolonged standing, a tendency to faint, chest pain, cool, sweaty extremities, migraine-like headache, pain in the back of the neck or shoulders, heat



POTS has many potential causes.

intolerance, chronic fatigue, exercise intolerance, shortness of breath on exertion, and panic/anxiety. At least some of these symptoms are thought to reflect increased effects of the *catecholamines, norepinephrine (noradrenaline)* or e*pinephrine (adrenaline),* in the heart, from overactivity of the *sympathetic nervous system* or *adrenomedullary hormonal system,* or both.

Most cases occur in relatively young (14-45 years old) women (female:male ratio about 5:1).

Postural Tachycardia Syndrome (POTS)

- *Mainly young adult women*
- *Too rapid pulse rate during standing*
- *Several non-specific associated problems (inability to tolerate prolonged standing, fatigue, faintness, chest pain, heart "flip-flops," heat intolerance, exercise intolerance, tendency to panic)*
- *Variable outlook, can improve*
- *Not life-threatening*

Some investigators view *POTS* as synonymous with *chronic orthostatic intolerance.* As discussed later, the condition has features also suggestive of *hyperdynamic circulation syndrome* or "*neurasthenia*." The many terms that have been used probably reflect different emphases by different research groups and large gaps in knowledge about the underlying mechanisms in individual patients.

The *orthostatic tachycardia* usually occurs without *orthostatic hypotension.* The finding of *orthostatic hypotension* does not exclude a diagnosis of POTS, however, and *delayed orthostatic hypotension* can occur in this condition.

POTS is a syndrome, not a single disease, and can have any of several causes.

Most *postural tachycardia* is secondary to identifiable problems, such as side effects of medications or dehydration from chronic illness. When the cause is not readily identified, and the patient has other complaints discussed below, then the patient is thought to have *postural tachycardia syndrome,* or *POTS.*

The occurrence of a rapid pulse rate when a person stands is necessary but is not sufficient to diagnose *POTS.* The key word in *postural tachycardia syndrome* is the word, *"syndrome."* A *syndrome* is a set of symptoms that occur together. Patients with *POTS* not only have a rapid pulse rate when they stand up, they also have several other symptoms, such as *orthostatic intolerance,* chronic fatigue, heat intolerance, exercise intolerance, headache, chest pain, palpitations, neuropsychological complaints such as disturbed sleep, anxiety, or depression, and disability.

Trying to identify a specific cause in a particular patient with *POTS* can be a great challenge to clinicians. There are probably as many causes of a fast pulse rate as there are of a fever, and all the symptoms of *POTS* are not specific for any single disease.

Researchers have thought that usually in *POTS, sympathetic nerve* traffic to the heart is increased as a

compensation. The compensation could be for a decrease in the amount of blood returning to the heart or a decrease in the *total peripheral resistance* to blood flow when the patient stands up. Either situation could alter information from the *baroreceptors* to the brain, leading to a reflexive increase in *sympathetic nervous system* activity directed by the brain.

Low Blood Volume

There are many causes for a decrease in the amount of blood returning to the heart when a patient is standing. The possibility of *blood volume* depletion or excessive pooling of blood in the legs during standing up has drawn particular attention. Indeed, low *blood volume* was noted in the first case report of *POTS,* and the response, at least in the short run, to infused *normal saline* can be dramatic.

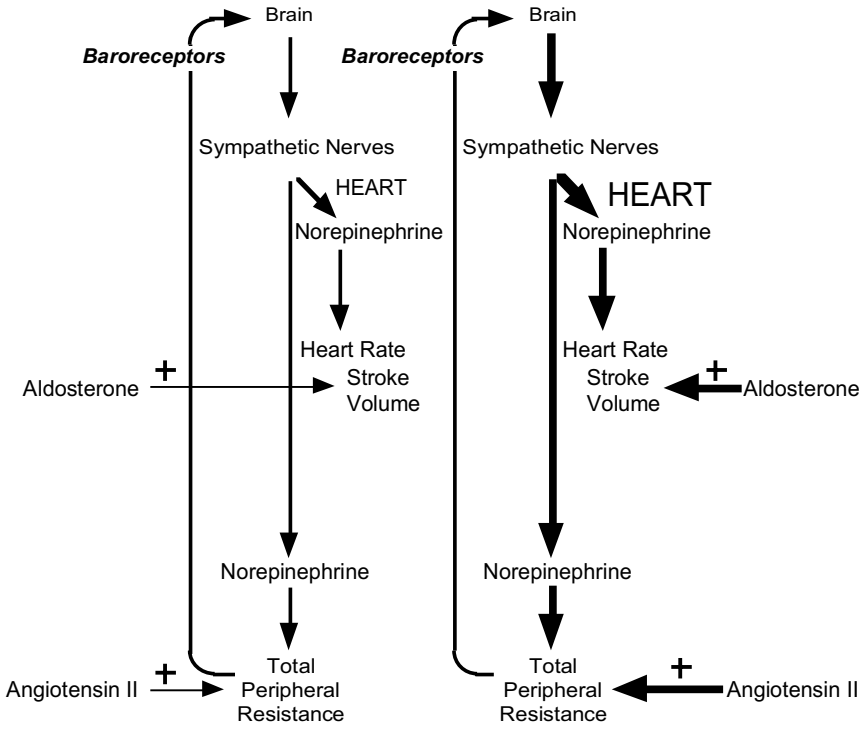
Low *blood volume* in turn can result from blood loss, from failure of the bone marrow to make an adequate number of red blood cells, or from failure of hormone systems such as the *renin-angiotensin-aldosterone* system. In addition, blood volume can fall while a person stands, due to leakage of fluid out of the blood vessels into the tissues *(extravasation).* Finally, an “effective” low blood volume can occur, when the blood pools excessively in the veins after a person stands, such as because of a lack of muscular “tone” in the vein walls.

Delayed orthostatic hypotension in *POTS* is also thought to result from a progressive, exaggerated decline in *blood volume* during prolonged standing, from leakage of fluid into the tissues through blood vessel walls *(extravasation).* Consistent with excessive blood pooling in the legs or lower abdomen during *orthostasis*, inflation of a *military antishock trousers (MAST) suit* reduces substantially the increase in heart rate in response to *orthostasis* in patients with *POTS.*

Neuropathic POTS

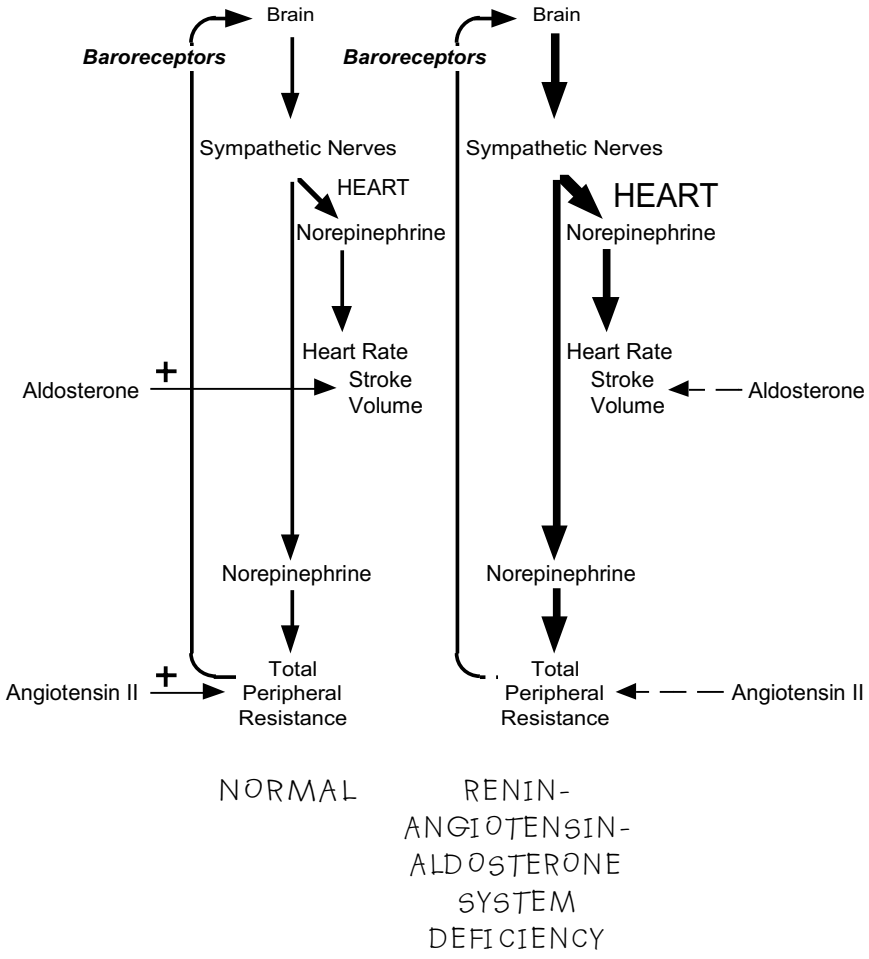
In *partial dysautonomia,* or *neuropathic POTS,* there is thought to be a patchy loss of sympathetic *innervation*, such as in the legs. When the patient stands up, the blood pools in the veins of the legs, and less blood returns to the heart, or else the arterioles fail to constrict, and the total resistance to blood flow decreases. In response to either or both of these abnormalities, the *sympathetic nervous system* supply to the heart would be stimulated reflexively.

There are other possible causes of decreased *total peripheral resistance* that might reflexively increase *sympathetic nervous system* traffic to the heart. For instance, any of several drugs block *receptors* for *norepinephrine* in blood vessel walls, and other drugs directly relax blood vessel walls.

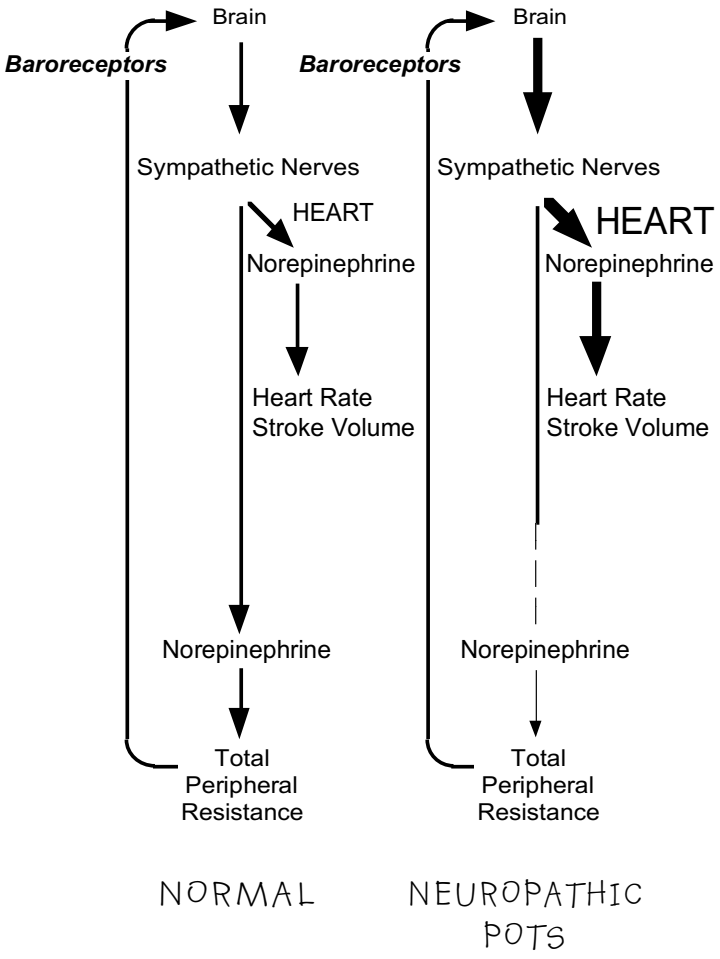


NORMAL DEHYDRATION or BLOOD LOSS

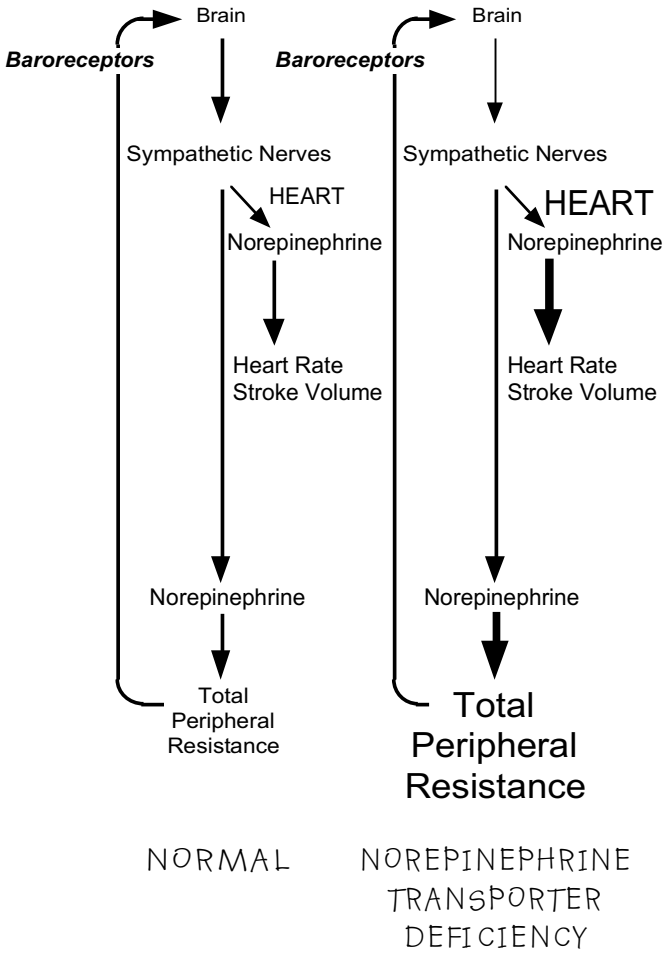
Dehydration, blood loss, or other causes of decreased blood volume can produce a condition that looks like POTS.



POTS can result from failure of a key system regulating salt balance and blood volume in the body, called the renin-angiotensin-aldosterone system.



In "neuropathic POTS," sympathetic nerves to the heart are thought to be overactive, as a compensation for loss of sympathetic nerves elsewhere.



Rarely, POTS can result from failure to inactivate norepinephrine, a key chemical messenger of nerves in the heart.

In rare patients, POTS results from deficiency of the *cell membrane norepinephrine transporter,* or *NET.*

Hyperadrenergic Orthostatic Intolerance

In *hyperadrenergic orthostatic intolerance,* the problem is thought to be a **primary** abnormality in the functioning or regulation of the *autonomic nervous system* itself.

For instance, in *acute baroreflex failure,* the brain does not respond appropriately to information from the cardiovascular system, and the *sympathetic nervous system* is activated inappropriately. In *acute baroreflex failure, orthostatic intolerance* is associated with large swings in blood pressure, because of the inability of the *baroreflexes* to keep the blood pressure in check, with episodes of extreme high blood pressure and fast pulse rate. Because of this failure, relatively minor stimuli can produce large increases in the activity of the *sympathetic nervous system.*

Another cause of *hyperadrenergic orthostatic intolerance* is decreased function of the *cell membrane norepinephrine transporter,* also called *NET deficiency.* The *cell membrane norepinephrine transporter* plays a key role in inactivating *norepinephrine.* Normally, most of the *norepinephrine* released from *sympathetic nerve terminals* is "recycled," by being taken back up into the nerve terminals. When the *transporter* is underactive, more *norepinephrine* is delivered to its *receptors* in the

heart and blood vessel walls for a given amount of *norepinephrine release,* producing an exaggerated increase in pulse rate and blood pressure in situations where the *sympathetic nervous system* is activated.

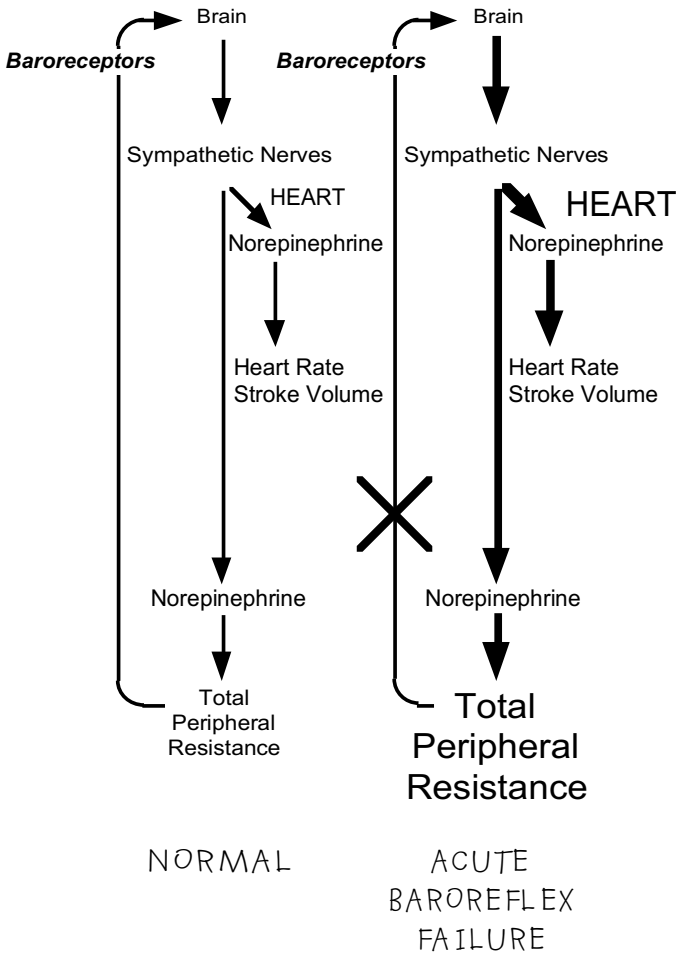
In a related syndrome, called the *hyperdynamic circulation syndrome,* the patients have a fast pulse rate all the time, variable high blood pressure, increased heart rate responses to the drug, *isoproterenol*, and increased plasma *norepinephrine* and *epinephrine* levels at rest and during provocative maneuvers. *ß-Adrenoceptor blockers* such as *Inderal*™ or *benzodiazepines* such as *Valium*™ improve the syndrome. It is unclear whether patients with this syndrome have an increased frequency of later development of established *hypertension.* Episodes of fast pulse rate and increased blood pressure can be associated with blotchy flushing of the face, neck, and upper chest.

"*Neurasthenia*" a term introduced in the late 1860s. refers to a syndrome initially described in Civil War soldiers. Also called *neurocirculatory asthenia,* the syndrome consists of a large number of symptoms, including breathlessness, *palpitations,* chest pain, dizziness, shortness of breath on exertion, fatigue, excessive sweating, trembling, flushing, dry mouth, numbness and tingling feelings, irritability, and exercise intolerance.

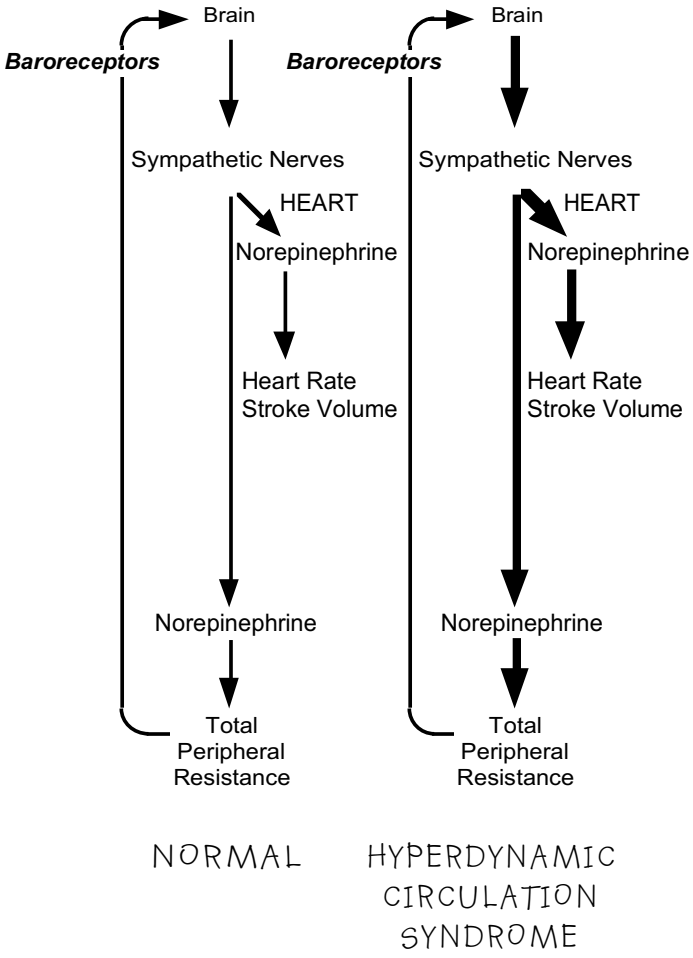
Most modern research about *neurocirculatory asthenia* has been conducted in Russia. Western cardiovascular researchers rarely use this term. The symptoms resemble

those in *POTS*, and as in *POTS*, the multiplicity of symptoms contrasts with a relative lack of signs, which all are non-specific—relatively fast pulse rate, relatively rapid breathing, facial and neck flushing, slight *tremor*, sweaty palms, a "functional" heart murmur, and hyperactive kneejerk reflexes, with generally normal resting blood pressure. Just as in *POTS* or the *hyperdynamic circulation syndrome*, in *neurasthenia* injections of *adrenaline* can evoke these symptoms. *ß-Adrenoceptor blockers* often normalize the cardiovascular findings without affecting the other symptoms and signs. Drugs such as *caffeine* can evoke fast pulse rate, increased ventilation, tremor, and sweatiness in patients with *neurocirculatory asthenia.*

In another related condition, *inappropriate sinus tachycardia,* the heart rate is increased to 100 beats per minute or more, even under resting conditions. *Radiofrequency ablation* of the *sinus node,* the heart's pacemaker area, is considered for patients with *inappropriate sinus tachycardia* who are resistant to treatment with medications.



Failure of the baroreflex can produce a condition that looks like POTS.



The hyperdynamic circulation syndrome can cause POTS.

As discussed below, the *POTS* syndromes differ from *neurocardiogenic syncope (neurally mediated syncope),* in that patients with *neurocardiogenic syncope* have inhibition, rather than stimulation, of the *sympathetic nervous system,* at least during acute episodes. Patients with *POTS* often have increased plasma levels of *norepinephrine,* the chemical messenger of the sympathetic nervous system, especially when they are standing up. Indeed, according to one suggestion, criteria for diagnosing *chronic orthostatic intolerance* include an upright plasma *norepinephrine* level of 600 pg/ml or more; however, whether increased sympathetic nervous outflows constitute a primary abnormality or compensatory response usually is unknown in an individual patient.

In general, one would predict that if the *orthostatic tachycardia* were primary, then treating it would help the patient, but if the *orthostatic tachycardia* were secondary, then treating the problem would not help the patient. Keeping this principle in mind can help to understand how one patient may feel better from treatment with a beta-blocker, which forces the pulse rate to go down, while another may not feel better at all, even though the pulse rate has decreased to the same extent.

Treatment of POTS should be tailored to the individual patient.

The first step in management of *chronic orthostatic intolerance* is to search carefully for common, reversible

causes, such as *diabetes*, weight loss, prolonged bed rest, debilitating diseases, and medications.

Medical treatments for *POTS* generally have attempted to increase *blood volume,* such as using Florinef™ and liberal salt and water intake, injections of *erythropoietin,* or infusions of saline intravenously; block fast pulse rates, such as using *ß-adrenoceptor blockers* or *sinus node ablation;* decrease exaggerated *norepinephrine* release, such as using *clonidine*, *-methylDOPA*, or *moxonidine;* or enhance *vasoconstriction*, such as using *midodrine, ergotamine,* or *octreotide.* Other treatments include venous compression hose, calf muscle resistance training, exercise training, or even insertion of a pacemaker.

Often these treatments, while helpful, do not bring the patients back to a sense of normal health. Over the course of months or even years, the patients can improve, or else they learn to cope with a chronic, debilitating, but not life-threatening disorder.

Neurocardiogenic Syncope

Syncope is sudden loss of consciousness associated with loss of muscle tone and the regaining of consciousness within a few minutes.

Syncope is sudden loss of consciousness (you black out) that is associated with loss of muscle tone (you go limp) and reverses rapidly (you wake up within minutes.)

Neurocardiogenic syncope, which is also called *vasovagal syncope, vasodepressor syncope, neurally mediated syncope,* and the *common faint,* is by far the most common cause of sudden loss of consciousness in the general population.

In *neurocardiogenic presyncope,* the patient feels like he or she will faint but does not actually lose consciousness.

Most patients with frequent episodes of *neurocardiogenic syncope* recognize early signs of

fainting coming on and are usually able to abort the episode before *syncope* actually occurs.

Neurocardiogenic syncope is most common in young adult women and in children.

Neurocardiogenic syncope is fainting. Neurocardiogenic presyncope is near-fainting but without actual loss of consciousness.

In mid-aged or elderly adults, *syncope* is more likely to be a sign of a heart problem (abnormal heart rhythm, abnormal conduction of electrical impulses in the heart, or heart valve problem) or *orthostatic hypotension*. In patients where neurocardiogenic syncope is a frequent problem, even between episodes the patients often feel unwell, with an inability to tolerate prolonged standing, chronic fatigue, headache, and chest pain.

Neurocardiogenic syncope can resemble *POTS.* Both disorders mainly involve young adult women, (although in children *neurocardiogenic syncope* may be more common than *POTS),* and both are associated with inability to tolerate prolonged standing, chronic fatigue, headache, and chest pain (although *POTS* may more commonly involve symptoms about multiple body systems). In both conditions the patients have a tendency to near-fainting or fainting spells, especially while standing. *Neurocardiogenic syncope* does appear to differ

from *POTS,* in that *neurocardiogenic syncope* does not feature a fast pulse rate.

Neurocardiogenic Syncope

- *Mainly young adult women or children*
- *Normal pulse rate during standing*
- *Can be associated with several non-specific associated problems (inability to tolerate prolonged standing, heat intolerance, fatigue, chest pain, heart "flip-flops," exercise intolerance)*
- *Variable outlook, can improve*
- *Not life-threatening*

Tilt-table testing can provoke a sudden fall in blood pressure, called *neurally mediated hypotension,* in patients with *POTS* or *neurocardiogenic syncope.* Regardless of the diagnosis, acute *neurally mediated syncope* may have the same mechanism. According to one proposal, the mechanism is from marked decreases in *sympathetic nervous system* outflow to the skeletal muscle in the limbs and probably several body organs, combined with increases in *adrenomedullary hormonal system* outflow and therefore high plasma *adrenaline (epinephrine)* levels.

The combination of loss of *sympathetic vasoconstrictor tone* and *epinephrine (adrenaline)*-induced relaxation of

blood vessels in skeletal muscle could decrease *vascular resistance* in skeletal muscle and in the body as a whole. It has been suggested that this combination explains the decreased *total peripheral resistance,* without a compensatory increase in the ejection of blood by the heart, the *cardiac output.* This combination characterizes *neurocardiogenic syncope.* Because of the fall in *total peripheral resistance,* without an increase in *cardiac output,* the *blood pressure* falls. The patient feels faint *(presyncope)* or actually loses consciousness *(syncope).*

Although physiological and hormonal changes that accompany *neurocardiogenic syncope* have received considerable research attention, studies so far have failed to identify predisposing factors. A decrease in the rate of *sympathetic nerve traffic* to the heart, or a restraint on release of *norepinephrine* from *sympathetic nerve terminals* in the heart, might cause a tendency to faint, by preventing compensatory increases in the force and rate of the heartbeat in response to a fall in *total peripheral resistance;* however, no published study so far has tested this idea.

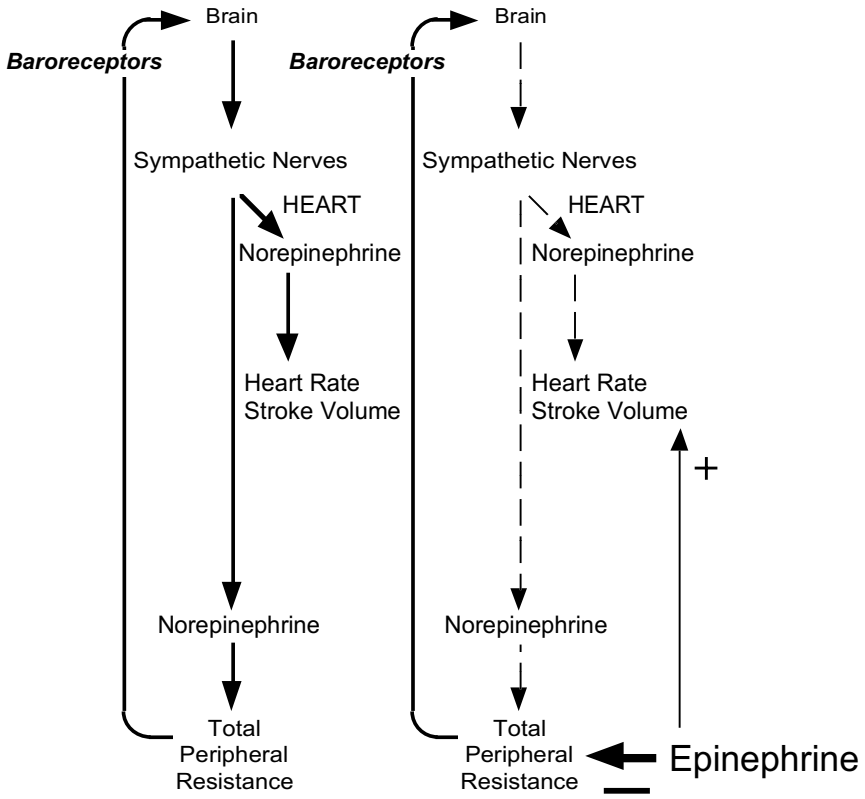
Reports about a high frequency of *neurocardiogenic syncope* and *neurally mediated hypotension* during provocative *tilt table testing* have supported the view that *chronic fatigue syndrome* often includes and may result from a form of *dysautonomia.*

The usual treatments for *neurocardiogenic syncope* are the same as for *POTS:* Florinef™ and liberal salt and water intake; *ß-adrenoceptor blockers; midodrine;* calf

muscle resistance training; exercise training; or insertion of a pacemaker.

Consistent with the notion that decreased *sympathetic nerve traffic* or decreased *norepinephrine* release predisposes to *neurocardiogenic syncope,* some patients note improvement with sympathomimetic amines such as *d-amphetamine* or *methylphenidate (Ritalin™).*

As in *POTS,* in *neurocardiogenic syncope,* there does not seem to be much risk of chronic cardiovascular disease.



NORMAL NEUROCARDIOGENIC SYNCOPE

Neurocardiogenic syncope involves an unusual pattern where before the acute episode, epinephrine (adrenaline) levels are high, and yet the sympathetic nervous system shuts down.