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.
Altered Autonomic Nervous System Function

- Worsening of another disease
- Harmful change in autonomic nervous system function
  - Compensatory activation
  - Abnormal autonomic nervous system function
    - Too active
      - Acute
      - Chronic
    - Too inactive
      - Acute
      - Chronic

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
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 Guinness 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 association 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 Denervation?

Yes

Central Neurodegeneration?

No

No

PAF

Yes

Parkinson’s

DLBD?

Anti-Nicotinic Receptor Ab?

Yes

Autoimmune
Autonomic Failure

No

MSA

? 

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.

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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.
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\textsubscript{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\textsuperscript{TM}, the most commonly used drug for Parkinson’s disease.

In the cerebellar form of MSA (MSA\textsubscript{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\textsubscript{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.

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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
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.
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.
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 epinephrine (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.
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. β-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. β-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 β-adrenoceptor blockers or sinus node ablation; decrease exaggerated norepinephrine release, such as using clonidine, α-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.

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.

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

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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.

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<th>Neurocardiogenic Syncope</th>
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<tr>
<td>• Mainly young adult women or children</td>
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<tr>
<td>• Normal pulse rate during standing</td>
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<tr>
<td>• Can be associated with several non-specific associated problems (inability to tolerate prolonged standing, heat intolerance, fatigue, chest pain, heart “flip-flops,” exercise intolerance)</td>
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<tr>
<td>• Variable outlook, can improve</td>
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<tr>
<td>• Not life-threatening</td>
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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; β-*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.
Neurocardiogenic syncope involves an unusual pattern where before the acute episode, epinephrine (adrenaline) levels are high, and yet the sympathetic nervous system shuts down.