

SYMPATHETIC STRESSORS AND SYMPATHETIC FAILURES

Any discussion of sympathetic involvement in “circulation”, and “vasodilation”, and “vasoconstriction” requires an understanding that there is no such thing as an overall sympathetic stress or sympathetic failure in any of these circulatory phenomena. Alpha-adrenergic and beta-adrenergic sympathetic reactivity cause entirely different, and sometimes exactly opposite reactions in the circulatory systems. So, norepinephrine, the major sympathetic neurotransmitter, has actions that are more dependent upon the alpha-adrenergic or beta-adrenergic receptor activated rather than the quantity or timing of norepinephrine itself. Additionally, adenosine, another sympathetic neurotransmitter, also influences vasoconstriction and vasodilation.

Here are some general rules:

- Alpha-adrenergic receptors, when activated by norepinephrine cause:
 - Vasoconstriction to the skin (White over Red Dermographics)
 - Vasoconstriction in mucosa and abdominal viscera
 - Vasoconstriction to muscles --- but --- that vasoconstrictive effect is overridden by the vasodilation of beta 2 adrenergic receptors in the blood vessels to muscles and the heart
- Beta-adrenergic (particularly beta 2) receptors, when activated by norepinephrine (and epinephrine) cause vasodilation to the muscles, and to the heart --- overriding the vasoconstrictive effects of the alpha 1 adrenergic receptors.
 - The vasodilation resulting from beta 2 adrenergic activation decreases peripheral vascular resistance ...
 - And also increases the force of myocardial contraction, and increases heart rate
 - Beta 1 adrenergic receptors also increase heart rate (by several mechanisms) and increase myocardial strength of contraction (stroke volume)
- As a general rule, norepinephrine preferably binds to alpha 1-adrenergic receptors rather than beta-adrenergic receptors. But that tendency that occurs at physiological rest is overwhelmed by the “fight or flight” sympathetic reflex that involves primarily beta 2 adrenal receptor activation, and is elicited more in response to epinephrine than to norepinephrine.

- Dissociation of sympathetic nerve activity in arm and leg muscle (--- not necessarily skin). -----Mental stress increases blood pressure and heart rate, and increases systemic forearm blood flow, but does not change calf blood flow. --- However --- Muscle Sympathetic Nerve Activity (MSNA) increases in the calf, but not in the forearm during mental stress. This increase in sympathetic nerve activity in the calf occurs despite the increased blood pressure, which would be expected to reflexly inhibit sympathetic nerve activity. During recovery from the mental stress, leg muscle sympathetic nerve activity remains elevated --- however, arm MSNA increases significantly during recovery after stress.

It is concluded that the sympatho-excitatory influence of mental stress overrides or inhibits baroreceptor control of leg sympathetic nerve activity, and that mental stress causes a dissociation of arm and leg muscle sympathetic nerve activity, with increased outflow to the leg, but not to the arm. The increased sympathetic stimulation in the leg during mental stress causes vasoconstriction, thus preventing the increase in calf blood flow; the reflex inhibition of sympathetic nerve activity as the blood pressure rises allows for an increase of forearm blood flow during mental stress.

ORTHOSTATIC CHALLENGE

- The baroreflex regulates blood pressure in adaptation to changes in body position, and fails in many autonomic disorders. The baroreflex regulates blood pressure by changing the heart rate (vagal component) and total peripheral resistance (beta-adrenergic component).
 - Standing up results in a reduction of venous return to the heart. When standing up (or undergoing head-up tilt), as blood volume shifts to dependent parts, most individuals experience a momentary reduction in systolic, diastolic, and pulse pressure.
 - Arterial and venous baroreceptors in the thorax and neck detect the change and send afferent impulses that synapse in the vasomotor center of the brain stem, triggering a sequence of responses --- efferent nerves travel to the heart (vagus nerve) to increase heart rate, and to arterioles (sympathetic fibers) to increase vascular resistance and blood pressure.
 - Baroreceptors are thus unloaded, and the baroreflex, by adjusting the heart rate (vagal component) and total peripheral resistance (sympathetic adrenergic component), prevents a drop or spike in blood pressure.

POTS (Postural Orthostatic Tachycardia Syndrome)

Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by excessive tachycardia during orthostasis, with a heart rate increasing more than 30 beats per minute or sustained heart rate of 120 or more during head-up tilt, but in the absence of significant orthostatic hypotension --- a drop in systolic blood pressure of less than 20 and/or in diastolic blood pressure of less than 10). [Of course, in NUTRI-SPEC testing, any drop in systolic or diastolic pressure, or a drop in pulse pressure, indicates clinically significant orthostatic failure.] Upon standing or head-up tilt, patients develop dizziness, fatigue, headache, and/or anxiety.

- Normal baroreflex physiology involves increased heart rate, increased vascular sympathetic nerve activity, and peripheral vasoconstriction in response to the decreased venous return during upright posture. It is not clear whether the excessive tachycardia with orthostasis in POTS patients is the cause or the consequence of one or more abnormal steps in the baroreflex pathway.
- Peripheral vasoconstrictor responses are important predictors of successful orthostasis. If POTS patients have decreased sympathetic responses to orthostasis, the augmented tachycardia in these patients may be a compensatory response in the face of decreased peripheral vasoconstriction.
 - One study reports a higher frequency of Muscle Sympathetic Nerve Activity in POTS patients at rest, with smaller changes in sympathetic nerve activity with 75° head-up tilt. These data are consistent with the idea of decreased sympathetic responsiveness, i.e., smaller change with tilt in patients vs. controls. In other words, a higher resting sympathetic tone allows for less of a sympathetic surge in response to orthostasis.
- There is no significant difference between POTS and controls in baseline Muscle Sympathetic Nerve Activity (MSNA), nor diastolic blood pressure, but POTS patients have lower resting systolic blood pressure and higher resting heart rate.
- In response to Valsalva maneuver, POTS patients have a greater excitatory response of Muscle Sympathetic Nerve Activity.
- Valsalva maneuver causes a smaller than normal decrease in diastolic blood pressure during the second phase of Valsalva maneuver as the result of the increased sympathetic reactivity induced.
- Valsalva maneuver does not cause a significant difference in heart rate response in POTS patients.

- In response to 30° head-up tilt, POTS patients have a significantly greater Muscle Sympathetic Nerve Activity (MSNA) response, and an exaggerated response to 45° head-up tilt.
- The heart rate response to head-up tilt was significantly greater in POTS patients at both 30° and 45° of head-up tilt.
- Summary of findings in POTS patients is that they have significantly augmented sympathetic response to both Valsalva maneuver and to orthostatic challenge with head-up tilt.
- The augmented sympathetic excitation may be a compensatory response to dysfunction in one or more cardiovascular control mechanisms necessary for normal baroreflex responses. --- For example --- there is evidence that POTS patients have decreased vasoconstrictor responses to orthostasis. However, the data suggests that the decreased vasoconstriction is not the result of decreased sympatho-excitation. Possible sources of dysfunction include decreased norepinephrine release from vascular sympathetic nerve endings, decreased postsynaptic adrenergic responsiveness, and/or decreased production of noradrenergic vasoconstrictors such as angiotensin II.
- Studies show a decreased norepinephrine release, and that response deficit occurred selectively in the legs --- even though POTS patients tend to have greater systemic plasma norepinephrine concentrations during orthostasis. Such chronic repeated elevations in plasma norepinephrine could lead to receptor desensitization and result in decreased adrenergic vasoconstrictor responsiveness. If blood vessels of POTS patients exhibit less vasoconstriction to a given level of adrenergic stimulation, increased sympathetic activity could be a compensatory response in an attempt to normalize vasoconstriction. --- Yet --- studies show that patients with orthostatic intolerance have similar systolic blood pressure responses to phenylephrine, yet other evidence suggests decreased norepinephrine release from sympathetic neurons in POTS patients, but does not support impairment of pressor responses to adrenergic agonists in POTS.
- Impairment of renin-angiotensin may also contribute to decreased vasoconstrictor response to orthostasis in POTS. In addition to being a direct vasoconstrictor, angiotensin II increases norepinephrine release from adrenergic nerve terminals and augments the postsynaptic response. In normals, plasma renin activity increases in response to orthostatic challenge, but this response may be decreased in some POTS patients.
- Another potential area of dysfunction for which exaggerated sympatho-excitation could be an attempted compensation is increased venous pooling and/or capillary filtration during orthostasis. It is interesting that the

increased sympatho-excitatory response in POTS patients translates into better maintenance of diastolic blood pressure during the Valsalva maneuver but not during head-up tilt compared with control subjects.

- This failure during head-up tilt indicates that the increased heart rate and MSNA responses in POTS patients are necessary to maintain arterial pressure --- and --- the one condition that is present during head-up tilt but not during the Valsalva maneuver is gravity-induced venous pooling in the lower limbs. Excessive venous pooling and/or capillary filtration in the legs would result in a smaller effective circulating plasma volume and a greater requirement for sympatho-excitation to maintain arterial pressure. There is significantly greater venous pooling during orthostasis in POTS patients, and external application of pressure to the legs and abdomen significantly improves their orthostatic tachycardia. It is also found that the increase in calf volume with head-up tilt is significantly greater in POTS, which suggests increased venous pooling and/or capillary permeability.
- SUMMARY: Sympathetic responses to baroreflex stimuli are augmented in POTS. These augmented responses likely represent a compensatory response to other cardiovascular impairments that affect blood pressure regulation during orthostasis --- including:
 - diminished norepinephrine release
 - decreased responsiveness of the renin-angiotensin system
 - increased venous pooling and/or capillary permeability

Sympathetic Orthostatic Failure and Idiopathic Edema (Streeten)

Head-up tilt gives an orthostatic and thus a baroreflex challenge by using gravity to decrease venous return and cardiac output.

Sympathetic adrenergic failure is graded on the basis of degree of systolic blood pressure fall during tilt:

- There is an increase in capillary wall permeability.
- There are changes in capillary diffusion area, perhaps associated with excess dilation of precapillary sphincters.
- Orthostatic edema --- the upright posture is an important contributor to the excessive transudation in over 80% of cases.

- Hypoalbuminemia is more commonly the result than the cause --- albumin leaks out through the excessively permeable capillaries.
- Rarely, is elevated capillary hydrostatic pressure the cause.
- There are not abnormalities of lymphatic flow.
- The majority of patients have excessive orthostatic sodium retention associated with an excessive orthostatic fall in GFR (Glomerular Filtration Rate), frequently associated with excessive renal tubular reabsorption of the subnormal filtered sodium load because of orthostatic hyperaldosteronism.
 - Hyperaldosteronism has responded to the use of Spironolactone.
- 30-40% of patients have orthostatic water retention, with the inability to excrete more than 55% of a 20 ml/kg water load during 4 hours in the upright posture.
 - There may be excess vasopressin (Posterior Pituitary Anti-Diuretic Hormone).
 - Ethanol is an inhibitor of vasopressin release, and, in these cases, will restore normal orthostatic excretion of the water load.
- There is often reduced dopamine excretion.
- Sympathomimetic amines (ephedrine, phenylephrine, and especially dextroamphetamine) are the only agents that will significantly reduce the excessive weight gain from morning to evening, by mechanism that prevents excessive capillary transudation and pooling.
- Extreme orthostatic hypotension = systolic drop greater than 30; orthostatic failure = systolic drop 10-30, and sympathetic sudomotor failure.
- Blood pressure changes during the Valsalva maneuver will detect sympathetic vasoconstrictor failure with greater sensitivity than do orthostatic blood pressure findings.
 - Heart Rate changes may be better indicators than blood pressure changes.
- The measure of cardiovascular parasympathetic function involves the analysis of heart rate variability, while the measure of cardiovascular sympathetic function involves blood pressure response to physiological stimuli such as orthostatic changes and response to the Valsalva Maneuver.

- The heart rate response to deep breathing is dramatically impaired in patients with orthostatic hypotension.

ISOMETRIC CHALLENGE

- Isometric exercise is accompanied by increases in heart rate, blood pressure, and Muscle Sympathetic Nerve Activity (MSNA). --- Two mechanisms explain these responses. First, is a pressor reflex originating in the sensory receptors of a contracting muscle that are sensitive to ischemic metabolites generated during the muscle contraction. The second mechanism for autonomic adjustment to isometric exercise is central command, which refers to activation of the cardiovascular centers by descending neural pathways.

During sustained isometric hand grip at 30% maximal voluntary contraction, heart rate and blood pressure increase during the first minute of hand grip, while muscle sympathetic nerve activity increases not until the second minute. The increased muscle sympathetic nerve activity in the leg in the second minute is caused by the chemically sensitive muscle afferents; the increased heart rate and blood pressure in the first minute is caused by central command. --- That central command increases the heart rate but actually inhibits muscle sympathetic outflow in the leg.

- Muscle sympathetic activity does not increase during arrested circulation, so the muscle sympathetic stimulation resulting from isometric contraction is not due to ischemia, but by some factor associated with muscle work that stimulates excitatory muscle afferents.
- Central command produces opposite affects on heart rate and muscle sympathetic activity. --- While the heart rate goes up in the first minute or isometric contraction, the MSNA does not increase at all. During the second minute, the heart rate stays elevated but does not increase further, while MSNA increases dramatically. These dissociated autonomic effects result primarily from centrally mediated parasympathetic withdrawal during the first minute, as opposed to sympathetic stimulation. Parasympathetic inhibition not only causes the tachycardia, but inhibits MSNA.
- MSNA response to sustained muscle contraction results from the balance between the excitatory influence of chemically sensitive muscle afferents and the inhibitory influence of central command.
- Hemodynamic findings suggest that the sympatho-excitatory influence of muscle afferents is comparable in the arm and in the leg, but that the vasodilator influence of central command is greater in the arm. Some

researchers suggest that this centrally mediated vasodilator influence is cholinergic in nature, while others suggest that it is beta-adrenergic. A third possibility is that it involves inhibition of sympathetic vasoconstrictor activity.

Differential activation of sympathetic discharge to skin and skeletal muscle during static hand grip exercise: Sympathetic outflow to skin of the resting limb shows an initial burst of activity preceding the onset of tension development, and is followed by a sustained increase in sympathetic activity throughout the exercise. Sympathetic outflow to resting muscle shows a slow pattern of response with a latent period between the onset of exercise and the onset of sympathetic activation. It is concluded that during moderate levels of static exercise, sympathetic activation of skin is predominantly influenced by a central motor command, while sympathetic activation of muscle is driven mainly by feedback from metaboreceptor afferents in the working muscle.

- Baroreceptor afferents do not regulate sympathetic vasoconstrictor outflow to the cutaneous circulation. During upright posture at normothermia, cutaneous vasoconstriction is mainly driven by a local reflex. Assumption of the upright posture increases skin vascular resistance, and this increase is abolished when increased vascular transmural pressure is avoided by elevating the arm.
 - An upright posture with the arms dependent causes a 2-3-fold increase in skin vascular resistance. Even in the supine position, passive movement of the arm into a dependent position to activate veno-arteriolar reflexes alone evokes an increase in skin vascular resistance which approximates the response to normal upright posture. (--- Does a significantly less Red Dermographics response on the lower arm compared to the upper arm constitute an indicator of sympathetic activity?)
- Sustained hand grip causes vasoconstriction in legs but vasodilation in the contralateral arm, whereas Sympathetic nerve activity increases similarly in both radial and peroneal nerve during this stimulus. These findings may relate to the different balance in the legs vs. the arms between alpha-mediated vasoconstriction and beta-mediated vasodilation. Beta-mediated vasodilation is significantly lower in legs compared with arms. Thus, there is a dissociation between norepinephrine spillover and vascular responses to sympathetic stimulation in lower limbs characterized by a paradoxical decrease in local resistance despite increases in sympathetic activity.
 - At baseline, local vascular resistance is lower in the arms compared to the legs --- but after cold pressor stimuli, arm vascular resistance increases, while leg vascular resistance decreases. There is no

correlation between the norepinephrine spillover and the local vascular resistance.

- The maximal dilatory effect of beta-adrenergic receptors is greater in the arms than in the legs (435% vs. 160%). Alpha-adrenergic stimulation causes equal vasodilation in the arms and in the legs. The effect of beta-adrenergic receptors to induce vasodilation is significantly less in the legs than in the arms (Keep in mind that beta-adrenergics do not affect the skin, but are dilators to skeletal muscles (and coronary arteries)). The static hand grip-elicited increase in heart rate and blood pressure are associated with increased forearm but not calf blood flow. It is speculated that these differences in vascular responses between arms and legs are due to regional sympathetic cholinergic activation.
- Sustained isometric hand grip increases sympathetic nerve traffic in both arms and legs, even though it produces vasoconstriction in the legs but vasodilation in the contralateral arm. The mechanism for dissociation between nerve traffic and vascular responses is possibly related to sympathetically-mediated vasodilation involving a nitric oxide mechanism.
- It is postulated that the decreased sensitivity to beta-mediated vasodilation in legs contributes to the maintenance of vascular tone during the sympathetic activation (alpha-adrenergic) associated with upright posture.
- Taken together, the data suggests lesser sympathetic control of the arterial circulation of legs compared with arms.
 - There is less vasodilation in the leg compared to the arm in response to infusion with acetylcholine, and with substance P, and with sodium nitroprusside.
- The arterial vessels within the arms and legs are exposed to different hydrostatic pressures and blood flow demands, and so arterial reactivity differs in the arms and legs. There is greater blood flow response to vasodilator stimuli in the arms, and greater sympathetically-mediated vasoconstrictor responsiveness in the legs. Beta-mediated vasodilation is significantly lower in legs compared with arms. The paradoxical decrease in local resistance despite increases in sympathetic activity cannot be explained by differences in adrenergic receptor responses.

VALSALVA MANEUVER

[NUTRI-SPEC Testing does not utilize the Valsalva Maneuver to evaluate Sympathetic/Parasympathetic Imbalance for the same reason Hyperventilation is not used as an Acid/Alkaline Imbalance Test. These procedures are traumatic to patients. Nevertheless, the research literature on these tests affirms the validity of our tests and analysis.]

Using the Valsalva Maneuver to test sympathetic tone: maintaining an expiratory pressure of 40 mmHg for 15 seconds is a means of employing the Valsalva maneuver to create a sustained increase in intrathoracic pressure followed by its abrupt release. This increase and release of thoracic pressure causes a 4-phase response in arterial pressure.

- The Valsalva Ratio is the ratio between the highest heart rate reached in Phase II of the Valsalva maneuver and the lowest heart rate of Phase IV.
- The Valsalva maneuver increases intrathoracic pressure, reduces preload, which activates reflex vasoconstriction. Valsalva maneuver has 4 phases.
 - Phase I is a transient rise in blood pressure due to increased intrathoracic and intra-abdominal pressure which causes a mechanical compression of the aorta.
 - Early Phase II is a falling blood pressure due to the reduced venous return and stroke volume, which results in a fall in cardiac output in spite of tachycardia caused by withdrawal of cardiovagal influence. The baroreflex response to this fall in blood pressure is by an increase of efferent sympathetic discharge to muscle and an increase in plasma norepinephrine, so the total peripheral resistance increases. Within 4 seconds, (the late Phase II) the fall in blood pressure is arrested.
 - Phase III is the end of the Valsalva maneuver, with a sudden fall in intrathoracic and abdominal pressure resulting in a transient fall in blood pressure, lasting 1-2 seconds.
 - In Phase IV, venous return and cardiac output have returned to normal, while the arterial vascular bed is still constricted, resulting in transient blood pressure overshoot. In the autonomic laboratory setting, with studies done on patients supine, Phase IV may be more dependent on cardiac adrenergic tone than on systemic peripheral resistance.
- In normals, Phase I consists of a blood pressure increase lasting 2-4 seconds and followed by a biphasic Phase II consisting of an early Phase II where blood pressure drops 2.4, then in late Phase II rises 19.2, then Phase III rises 31.4. After alpha-adrenergic blockade, the blood pressure decline in

early Phase II and rise in Phase IV are both attenuated. In patients with autonomic failure, the drop in early Phase II is exaggerated, there is no rebound in Phase III, and Phase IV merely returns to just below normal resting blood pressure level. In mild orthostatic hypotension, the drop in blood pressure in early Phase II is exaggerated, the rebound in Phase II is diminished, but there is an overshoot in Phase IV. Some patients exhibit presyncope symptoms related to the exaggerated and protracted reduction of blood pressure during Phase II. The most characteristic blood pressure change after administering propranolol was an attenuation of the Phase IV overshoot. Atropine (a muscarinic antagonist), exaggerated early Phase II almost as much as the alpha blocker and inhibited the late Phase II rebound, yet yielded a Phase IV increase in blood pressure about the same as controls. (Note that after atropine injection heart rate rose significantly from a baseline value of 68 to 95.)

- SUMMARY: Patients with orthostatic hypotension have attenuated heart rate response, indicating widespread alpha-adrenergic failure and exhibit Valsalva maneuver Phase II hypotensive response. An alpha-adrenergic blockade results in a marked reduction, of Phase II, confirming that its presence is mainly due to alpha-adrenergic activation. But of particular note is the increase, rather than reduction of Phase IV. These changes likely reflect a redistribution of blood under alpha-adrenergic blockade from the thorax to the extremities and the splanchnic bed, so that less blood remains to buffer the reduction in venous return.
- Beta-adrenergic antagonists dramatically attenuate the Phase IV pressor response, but with a lesser effect on Phase II than the alpha-adrenergic block. Phase IV overshoot is most dependent on cardiac sympathetic innervation, and early Phase II is most affected by peripheral sympathetic innervation.