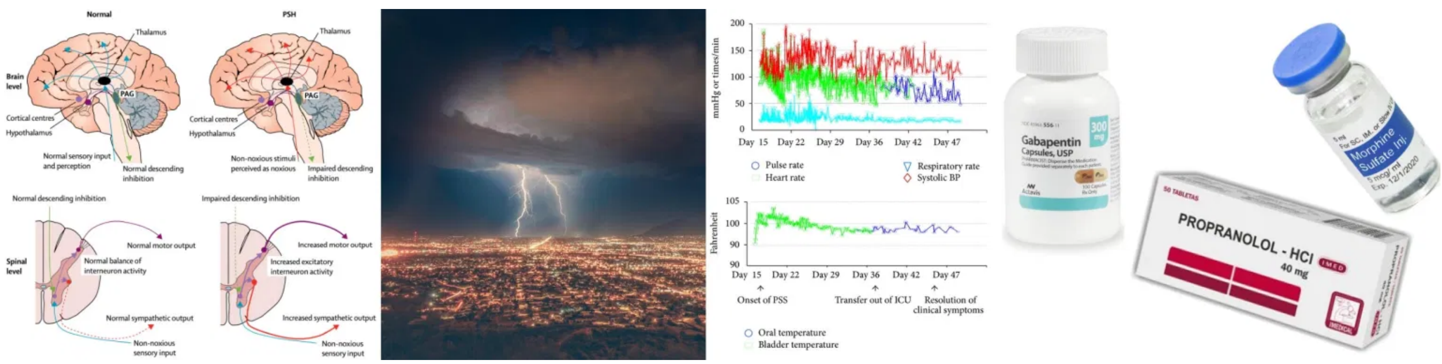
The Internet Book of Critical Care

Paroxysmal sympathetic hyperactivity (PSH)

May 29, 2021 by Josh Farkas



(https://emcrit.org/ibcc/psh/attachment/pshtop/)

CONTENTS

introduction

(back to contents) (#top)

basics

- Paroxysmal sympathetic hyperactivity (PSH) is a pattern of recurrent bursts of dysregulated sympathetic activity, resulting from severe brain injury. These episodes of sympathetic activation are short, dramatic, and often triggered by stimulation.
- PSH can be a challenging diagnosis, which may easily be confused with seizure, respiratory failure, withdrawal, or nonspecific agitation.
- PSH has previously been known by dozens of terms, for example:

- Sympathetic storming, autonomic storming.
- Episodic autonomic instability.
- Paroxysmal autonomic instability with dystonia.
- Diencephalic fits.

pathophysiology

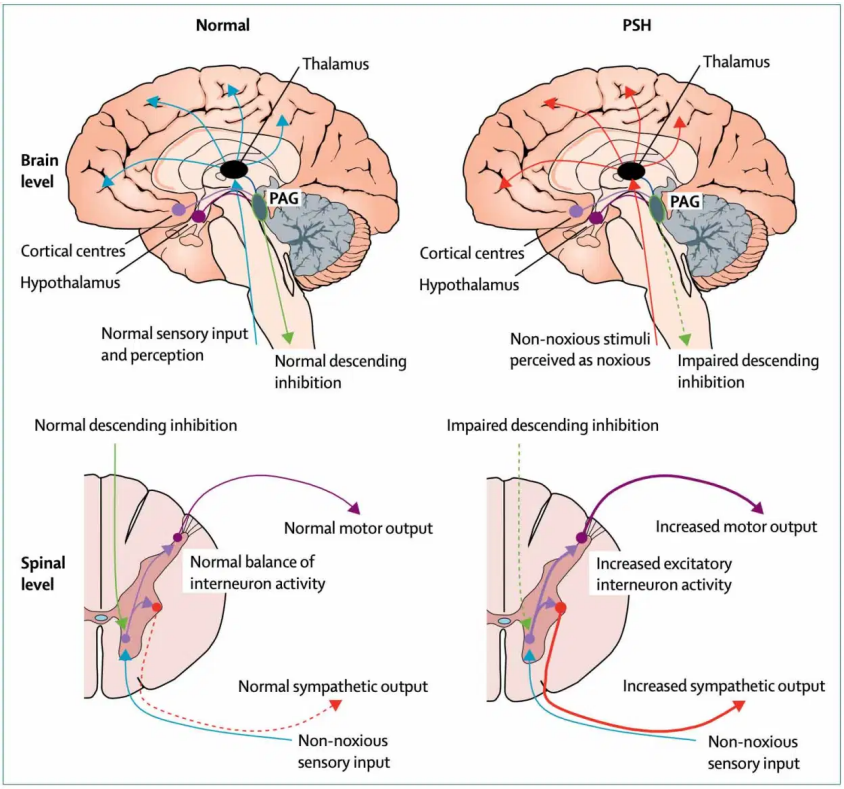


***Figure 2*: Excitatory:inhibitory ratio model of the pathogenesis of PSH**
In normal circumstances, various cortical, hypothalamic, thalamic, and other subcortical inputs modulate activity within brainstem centres—the PAG is shown here as one of the key brainstem hubs in this process. These brainstem nuclei provide inhibitory drive to spinal-reflex arcs, thereby maintaining balance between inhibitory and excitatory interneuron influences on motor and sympathetic efferents, allowing normal sensory stimuli to be perceived as non-noxious. In the excitatory:inhibitory ratio model of PSH, disconnection of descending inhibition produces maladaptive dendritic arborisation and spinal-circuit excitation, with non-noxious stimuli triggering increased motor and sympathetic output (spinally) and potentially becoming perceived as noxious (centrally).[35,36] PAG=periaqueductal grey. PSH=paroxysmal sympathetic hyperactivity.

Meyfroidt G, Baguley IJ, Menon DK PMID 28816118

(https://emcrit.org/ibcc/psh/attachment/pshphys/)

- Normally, descending inhibitory pathways from cortical inhibitor areas exert *negative*, *modulatory* activity on sympathetic centers in the diencephalon, brain stem, and spinal cord.(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/)) PSH results from a *loss* of these inhibitory pathways.
  - The precise neuroanatomic substrate is unclear. The closest correlate might be with damage to the white matter tracts in the posterior limb of the internal capsule and posterior corpus callosum (e.g., due to diffuse axonal injury following trauma).
  - Multiple cortical and subcortical areas are involved in modulation of sympathetic activity, so the development of PSH seems to require relatively diffuse or multifocal cerebral injury.(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/))
- Without inhibitory modulation from higher brain centers, sympathetic activity spirals out of control. This is analogous to *spinal reflexes* (e.g., triple flexion) which are normally inhibited by higher brain centers – but may become hyperactive due to inadequate suppression.
- Normally, inhibitory modulation from higher brain centers tempers how the spinal cord processes sensory information. Without this modulation, spinal cord remodeling may occur. This can create a positive feedback loop wherein *normal* sensations are perceived as *painful* (allodynia).(29939858 (https://pubmed.ncbi.nlm.nih.gov/29939858/)) This allodynia can cause relatively minor stimuli to trigger episodes of PSH.

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epidemiology

(back to contents) (#top)

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pathologies which commonly cause PSH

- 80% are due to **traumatic brain injury**.
  - The rate of PSH among patients with severe traumatic brain injury may be on the order of ~20%.(29939858 (https://pubmed.ncbi.nlm.nih.gov/29939858/))
  - PSH is especially associated with diffuse axonal injury.
- 10% are due to **anoxic brain injury**.
- 5% are due to **stroke** (especially large intracranial or subarachnoid hemorrhage).
- 5% are due to other pathologies, including:
  - Acute hydrocephalus.
  - Tumors.
  - Hypoglycemic brain injury.
  - Infection (e.g., encephalitis).
  - Cerebral fat embolism syndrome.
  - Autoimmune encephalitis.

risk factors for the development of PSH

- Severity of initial injury.
- Younger age.
- Male sex.

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clinical findings

(back to contents) (#top)

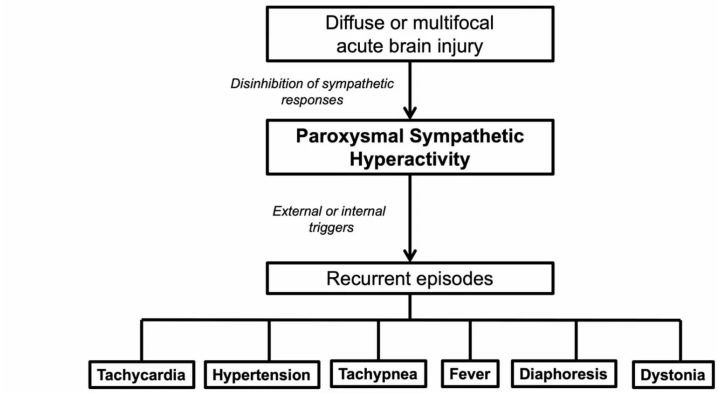

Fig. 1 Basic pathophysiology and manifestations of paroxysmal sympathetic hyperactivity.

Scott RA and Rabinstein AA, PMID 32906174

(https://emcrit.org/ibcc/psh/attachment/pshoutline/) **clinical context & pattern**

- PSH usually occurs in the context of *severe* and *diffuse* brain injury that initially causes prolonged unconsciousness (e.g., traumatic brain injury or anoxia – more on this above).
- PSH most often begins within the first two weeks after initial brain injury. Episodes may become more obvious as opioids and sedatives are weaned off.
- On average, PSH episodes may occur roughly 1-3 times per day.
- PSH usually resolves within a year.(29939858 (https://pubmed.ncbi.nlm.nih.gov/29939858/))

episodes of PSH are marked by:

- (1) Sympathetic hyperactivity:
  - Tachycardia (~98% of cases), hypertension.
  - Tachypnea (which may manifest as ventilator dyssynchrony).
  - Diaphoresis.
  - Pupillary dilation.
  - Fever can occur.
- (2) Motor activity:
  - Posturing (typically symmetric) in <40% of cases.
  - Agitation can occur.

chronicity of individual episodes

- Episodes have a rapid onset, often due to an identifiable trigger (e.g., endotracheal tube suctioning, repositioning, pain, or bladder distension).
- Episodes last up to ~30 minutes, after which they will abate spontaneously.(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/))
- If IV morphine causes resolution of the episode, this supports the diagnosis of PSH.
- In between episodes, there should be nearly complete resolution.

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differential diagnosis

(back to contents) (#top)

The differential diagnosis will vary, depending on any individual patient's symptomatology. The first episode of PSH may be the most confusing, before it becomes clear that a recurring pattern is being established. For example, the initial episode of PSH may clinically resemble herniation (with hypertension and symmetric, bilateral posturing).

some other causes of *repeated* episodes of sympathetic activation

- Tonic seizures may cause hypertension and tachycardia.
- Plateau waves due to ICP elevation, although these don't generally cause profuse diaphoresis (more on this *here (https://emcrit.org/ibcc/icp/#plateau_waves)*).(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/))
- Episodes of uncontrolled pain or agitation.
- Episodes of dyspnea, due to respiratory failure.
- Withdrawal from opioids or benzodiazepines (this can be confusing, because PSH often arises as sedatives and analgesics are being weaned off).
- Autonomic dysreflexia due to spinal cord injury. This is very similar to PSH, but involves a lesion in the spinal cord (rather than the white matter of the brain). Unlike PSH, episodes may be associated with *bradycardia*.

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approach to the diagnosis

(back to contents) (#top)

There is no test to prove the presence of PSH. Consequently, evaluation consists predominantly of excluding alternative diagnostic possibilities.

exclusion of alternative diagnoses may involve:

- Exclusion of seizure with video EEG.
- Evaluation for structural brain lesion with neuroimaging and ultrasound (to screen for intracranial pressure elevation).

consider the consensus definition

- Below is a table developed by expert consensus to use as a definition for paroxysmal sympathetic hyperactivity.(24731076 (https://pubmed.ncbi.nlm.nih.gov/24731076/))
- This table isn't necessarily intended as a final arbiter of the diagnosis, but it does provide a systematic way of approaching the diagnosis.

TABLE 1. PAROXYSMAL SYMPATHETIC HYPERACTIVITY—ASSESSMENT MEASURE

Clinical Feature Scale (CFS)

	0	1	2	3	Score
Heart rate	<100	100–119	120–139	≥140	
Respiratory rate	<18	18–23	24–29	≥30	
Systolic blood pressure	<140	140–159	160–179	≥180	
Temperature	<37	37–37.9	38–38.9	≥39.0	
Sweating	Nil	Mild	Moderate	Severe	
Posturing during episodes	Nil	Mild	Moderate	Severe	
			CFS subtotal		

Severity of clinical features	Nil	0	
	Mild	1–6	
	Moderate	7–12	
	Severe	≥13	

Diagnosis Likelihood Tool (DLT)

Clinical features occur simultaneously	
Episodes are paroxysmal in nature	
Sympathetic over-reactivity to normally non-painful stimuli	
Features persist ≥3 consecutive days	
Features persist ≥2 weeks post -brain injury	
Features persist despite treatment of alternative differential diagnoses	
Medication administered to decrease sympathetic features	
≥2 episodes daily	
Absence of parasympathetic features during episodes	
Absence of other presumed cause of features	
Antecedent acquired brain injury	
(Score 1 point for each feature present)	DLT subtotal

Combined total (CFS + DLT)			
PSH diagnostic likelihood	Unlikely	< 8	
	Possible	8–16	
	Probable	> 17	

(https://emcrit.org/?attachment_id=481606)

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supportive care

(back to contents) (#top)

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avoid triggers of PSH

- Avoid the use of antipsychotics.(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/))
- Avoid triggers as able (e.g., bladder distention, endotracheal suctioning).

best supportive care

- Nutritional support: Patients may have increased resting energy expenditure up to two or three times baseline, which can lead to substantial weight loss.(29939858 (https://pubmed.ncbi.nlm.nih.gov/29939858/))
- Fluid resuscitation: Profuse diaphoresis can promote volume depletion.
- Fever management: These fevers do not seem to be driven by inflammatory sensors in the hypothalamus, so they may not be responsive to acetaminophen. If the fever poses a risk of secondary brain injury, *physical cooling* techniques may be required (e.g., a cooling blanket or even an adaptive external cooling device).

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overview of medical therapy

(back to contents) (#top)

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concept #1 – multimodal therapy

- There is no single "silver bullet" medical therapy for PSH.
- Most patients will require *multimodal therapy*.(28816118 (https://pubmed.ncbi.nlm.nih.gov/28816118/))
  - Multiple medications with complementary mechanisms of action are combined.
  - Using *moderate* doses of *multiple* medication classes allows for synergistic efficacy, while avoiding the toxicity that would result from using *high* doses of any *single* medication.

concept #2 – abortive vs. preventative therapy

- Although there is some overlap, different medications are optimal for *aborting* an episode of PSH versus *preventing* future episodes. Patients will often require a combination of scheduled preventative therapies plus abortive therapies as needed.
- Ideal properties of a medication used to abort an episode of PSH:
  - The medication may be given *intravenously* with *rapid* onset (ideally within minutes).
  - PSH episodes will resolve on their own within <30 minutes. Therefore, in order for any abortive medication to be useful, it must be *readily available*.
- Ideal properties of a medication used to prevent future episodes of PSH:
  - These medications may be used on a *chronic* basis, without provoking excessive amounts of tolerance or withdrawal.
  - Often these are *oral* medications, which can be continued on a long-term basis (e.g., following ICU discharge). One exception is that intravenous dexmedetomidine may be used as a preventative therapy, but this may be transitioned to oral clonidine for longer-term efficacy (both dexmedetomidine and clonidine are central alpha-agonists, with a similar mechanism of action).

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abortive therapy

(back to contents) (#top)

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rationale for aborting an episode of PSH

- (1) Diagnostic role – Responsiveness to morphine may also help support the diagnosis of PSH, in situations where this is unclear.
- (2) Therapeutic role – Uncontrolled paroxysmal sympathetic hyperactivity can cause hyperthermia and hypertension leading to secondary brain injury, as well as discomfort. The urgency with which an episode requires treatment depends on its severity.

opioids

- The greatest experience is with morphine, typically at doses of ~2-8 mg IV (but occasionally requiring doses up to 15 mg). Morphine is probably the most effective and preferred agent. If morphine is ineffective in stopping an episode, this should suggest the possibility of an alternative diagnosis.
- Fentanyl may offer the advantage of faster onset, at doses of 25-100 mcg IV.(32476028 (https://pubmed.ncbi.nlm.nih.gov/32476028/))

propofol

- This is an excellent option for a patient who is intubated.
- To abort an episode, a bolus of 10-20 mg of propofol may be used.(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/))

benzodiazepines

- These may be helpful (e.g., in patients with marked tolerance to opioids).
- The fastest onset may be obtained with IV diazepam (doses of 5-10 mg) or IV midazolam (doses of 2-5 mg).(32906174 (https://pubmed.ncbi.nlm.nih.gov/32906174/))

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preventative therapy

(back to contents) (#top)

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propranolol

- **General comment**: Propranolol is a front-line agent to prevent PSH. Propranolol is lipophilic and exerts direct effects on the brain, making it more effective than most other beta-blockers.
- **Indications/contraindications**: Propranolol is contraindicated in patients with bradycardia, decompensated heart failure, hypotension, or heart block.
- **Dose**:
  - Oral dosing is preferred, often beginning at a dose of ~40 mg PO q6hr. Uptitration as needed, within a range of 20-80 mg q4-8 hours.
  - Intravenous dose: Less information on this is available. 1 mg IV q6hr might be reasonable as a starting dose, with uptitration as clinically indicated. (30429730 (https://pubmed.ncbi.nlm.nih.gov/30429730/))

gabapentin

- **General comment**: Gabapentin may be useful here, with a potential to modulate allodynia and neuropathic pain that triggers episodes. An advantage of gabapentin is that it is often well tolerated for longer-term use. Another advantage of gabapentin is that it doesn't cause hypotension, facilitating its combination with propranolol or clonidine.
- **Indications/contraindications**: This is one of the most useful preventative medications. May be especially helpful for patients who also have *neuropathic pain*.
- **Dose**: Start with 300 mg TID. May rapidly uptitrate to a cumulative dose of 3,600 or 4,800 mg/day in patients with normal renal function.(25220846 (https://pubmed.ncbi.nlm.nih.gov/25220846/) , 28816118 (https://pubmed.ncbi.nlm.nih.gov/28816118/))

alpha-2 agonists (clonidine, dexmedetomidine)

- **General comment**: Centrally acting alpha-2 agonists may down-regulate sympathetic activity, via activity on both the brain and the spinal cord.
- **Indications/contraindications**:
  - (1) Most useful for patients with robust adequate heart rate and blood pressure in between episodes. Otherwise, there may be a risk of precipitating bradycardia or hypotension between episodes.
  - (2) These agents also have mild sedative effects, which may be beneficial for some patients.
  - (3) Patients who have responded favorably to IV dexmedetomidine may be transitioned to oral clonidine.
- **Clonidine dose**
  - If starting de novo, begin at a dose of 0.1 mg q8hr. May uptitrate to 0.1-0.3 mg q6-8 hours, for a maximal cumulative daily dose of 1.2 mg.
  - (28816118 (https://pubmed.ncbi.nlm.nih.gov/28816118/))
  - If transitioning from IV dexmedetomidine to PO clonidine: If the patient tolerated dexmedetomidine well, they are less likely to develop hypotension due to clonidine. Consequently, somewhat higher doses of clonidine may be used initially (e.g. 0.2-0.3 mg PO q6hr). More on this *here* (https://emcrit.org/ibcc/sedate/#oral_alpha-2_agonists) .
- **Dexmedetomidine dose**: Titrate to effect. Avoid boluses, as these may cause hemodynamic swings.

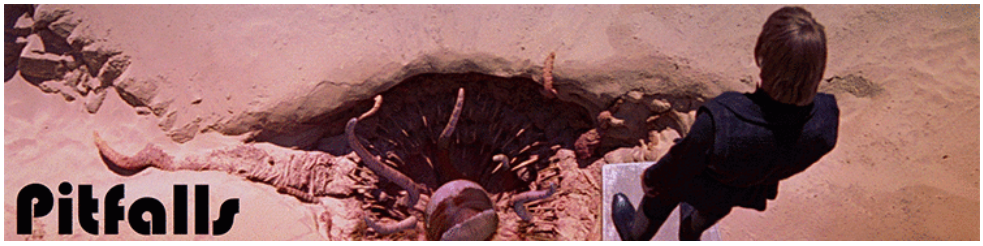
propofol

- Propofol infusion may be used for intubated patients.

- This isn't a viable *long-term* strategy, but it may be used while uptitrating other agents.

less desirable options

- Scheduled, long-acting benzodiazepines are an option (with limitations, including increased rates of delirium, tolerance, and reduced efficacy of benzodiazepines to abort episodes of PSH). If absolutely required, options might include clonazepam 0.5-2 mg PO q8hr or possibly diazepam 5-10 mg PO q8hr.
- Baclofen is another option (e.g., 5 mg PO q8hr, uptitrate as needed to a maximum dose of 80 mg/day).(28816118 (https://pubmed.ncbi.nlm.nih.gov/28816118/)) Similar to benzodiazepines, the long-term use of baclofen may be complicated by delirium, tolerance, and withdrawal.



(https://i0.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- If paroxysmal sympathetic hyperactivity isn't considered, then symptoms may be regarded as a manifestation of untreated pain or agitation. This may lead to inappropriate treatment with high doses of analgesics and sedatives.
- Be wary of trying to make the diagnosis of PSH in patients without an underlying cause.

references

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