

THE PATHOPHYSIOLOGY OF HICCUPS- A COMPREHENSIVE REVIEW

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Abstract: A hiccup is a sudden, repetitive involuntary contraction of the diaphragm and the intercostal muscles immediately followed by laryngeal closure. Hiccups are usually self-limiting, lasting up to a few minutes without any major clinical significance or the need for medical assistance. It may be the result of factors that trigger any of the three components of the reflex arc viz. the afferent limb, central limbic system or the efferent limb or any combination of neurotransmitters that assist the reflex arc. Despite its common occurrence, the pathophysiology and management of hiccups still remains unclear. Recent literature primarily consist of case reports which support the broad evidence of the numerous etiological factors and various drug treatments. Generally considered harmless, episodes of persistent or intractable hiccups may tend to have an underlying sinister pathology which may be easily overlooked. The etiopathogenesis has most often been attributed to lesions of the central and peripheral nervous system; with numerous documentations of other rare and unique case presentations which may be equally life-threatening. These cases require a thorough analysis of the symptoms and adequate investigations to arrive at a conclusive diagnosis. Therefore, the treatment modalities may encompass either pharmacological or non-pharmacological protocols or a combination of the two to effectively prevent persistent forms of hiccups that are capable of affecting the quality of life of the individual. This review aims to briefly discuss the epidemiology, pathophysiological mechanisms, etiological factors, investigations, diagnosis and the therapeutic modalities of hiccups.

Keywords: baclofen, hiccup centre, intractable hiccups, gastro-esophageal reflux disease, neurotransmitters, reflex arc

Introduction:

The term 'hiccup' or its scientifically appropriate 'singultus' was originally derived from the Latin word 'singult', referring to the act of catching one's breath or gasping while sobbing. By the late 16th century, the term 'hiccough' which was supposedly associated more often with coughing was gradually replaced with the modern-day 'hiccup'. [1] Hiccups are caused by the onset of repeated, involuntary, spasmodic contractions of the diaphragm and intercostal muscles. This coordinated inspiratory muscle contraction causes an abrupt, rapid rush of air into the lungs which is interrupted by closure of the glottis, resulting in the characteristic production of the 'hic' sound. [2] Hiccups are an uncommon medical complaint as they are benign or self-limiting, occurring anywhere between 4-60 times a minute. [3]

Evolutionary mechanisms:

Despite having no apparent physiological function in children and adults, prenatal ultrasound examinations and movements felt by pregnant mothers have shown hiccups occurring in utero, prior to reflexes of respiration or swallowing. This may suggest a preparatory role for the muscles of inspiration post-partum [4]. Interestingly, newborns hiccup 2.5% of the time with the reflex gradually waning away, [4] suggesting that this mechanism may indeed be a vestigial reflex. [5] But this theory may not be conclusive as the brief contraction of the respiratory muscles are insufficient to have any contributory role to respiration. [3] Investigators such as Straus et al have proposed that the development of the hiccup reflex may have evolved from the gill ventilation mechanism seen in lower vertebrates. [6] Controversy also surrounds theories that suggest that hiccups help to push out food boluses trapped in the esophagus. Such an event would be highly unlikely as a hiccup causes a drop in intra-thoracic pressure and this would cause the bolus to move further into the esophagus and cause a possible obstruction. [Fass] Another theory puts forward the notion that the hiccup may in fact be a precursor to the burping reflex to allow mammals to simultaneously suckle and release air trapped within the stomach, thereby increasing the gastric content of the nutrient medium. [3]

Epidemiology:

Hiccups can be broadly classified into three sub-types based on the duration that the hiccups last for. [8]

1. Acute hiccups are self-limiting usually resulting from rapid gastric distension due to extremes in the quantity or quality of food or beverages taken or even anxiety or stress. A transient episode would last for anywhere between a few seconds, minutes or hours but not exceeding beyond 48 hours. Some authors suggest recurrent hiccups are another form of acute hiccups where episodes last greater than transient hiccups, often with frequent repetition.[9]
2. Persistent or protracted hiccups are episodes that continue for more than 48 hours and are most likely to be associated with an underlying pathology. [10]
3. Intractable or chronic hiccups which may extend up to several days or months, and rarely even years. Over a hundred associated causes have been linked with these form of hiccups as documented by various case reports.[11] These conditions may in fact be life threatening with sequelae of depression, sleep deprivation, malnutrition to avoid triggering food or fluids and even death in very rare situations.[12]

Data regarding the incidence rates of patients of patients reporting with the chief complaint of persistent or intractable hiccups are rare and too few in between. In the United States alone, approximately 4000 cases of hiccup-related hospitalizations were recorded in 1999.[13] In a retrospective study conducted between the years 1995 and 2000, it was found that only 54 individuals out of 100,000 consecutive admissions were hospitalized due to hiccups.[10] The study also identified a 91% male predilection which was in accordance with an analysis performed among case-control studies; especially in men affected by an underlying central nervous system(CNS) pathology.[14] Among the numerous causes that have been listed as a pathology, the most frequent appear to be those related to the CNS[15] and, gastrointestinal tract (GIT) particularly esophageal cancers.[16,17]

Pathophysiology:

The hiccup reflex arc was first proposed by Bailey in 1943.[18] The reflex arc comprises of three components[19]:

1. Afferent limb: comprises of the vagal, phrenic and sympathetic nerves which contributes to the thoracic outflow in T6-T12. Somatic and visceral stimuli from the central and peripheral nervous systems travel via the afferent limb to be uploaded into the central limbic system. The afferent limb is believed to be variable among individuals and is also dependent on the degree of stimulus required to facilitate the reflex arc.[3]
2. Central processing unit: is presumed to be located in the medulla as well as certain areas between the brain stem and cervical spine between C3 and C5. On analysing electrophysiological function and muscle contraction, it can be concluded that the hiccup centre may be unique from the centres that regulate breathing.[20] Central neurotransmitters such as dopamine, gamma-aminobutyric acid (GABA) and serotonin [21] within the peri-aqueductal gray matter and subthalamic nuclei are major contributors in signal transduction in the reflex arc.[22] Other peripheral neurotransmitters such as histamine, adrenaline, noradrenaline and acetylcholine act on the respiratory muscles, diaphragm, glottis and GIT.
3. Efferent limb: includes the motor fibers of the phrenic nerve to the diaphragm and accessory nerves to the intercostal muscles. It also supplies the glottis, esophagus and scalene muscles but amongst these structures, the diaphragm is considered the most important.

When there is a disturbance occurring in the signalling pathway, an action potential is generated, culminating in a sequence of events where the protective response of the glottis is to close; resulting in the characteristic 'hic' sound. During laryngeal closure, other events that occur simultaneously are a sharp drop in intra-thoracic pressure, suppression of esophageal peristalsis, relaxation of the lower esophageal sphincter and the inhibition of innervation to the muscles responsible for exhalation.[3] Despite a lack of clarity in the hiccup reflex arc, investigators contribute the role of neurotransmitters as being the primary modulators. Among the central neurotransmitters, GABA has an inhibitory effect in the brain and spinal cord by altering the transmembrane potential. As GABA has abundant receptors, drugs such as barbiturates, benzodiazepines, ethanol and volatile anaesthetics like propofol act on the receptor site eliciting a hiccup,[18] which is a well established side-effect of these group of drugs.[2] Dopamine is a non-selective adrenergic agent found in the brain and GIT, playing an important role in the regulation of the endocrinal system, psychiatric disorders and Parkinsonism. Another central neurotransmitter, serotonin also acts as a hormone within the GIT, controlling both smooth muscle function and vasoconstriction of the gut and could explain why serotonin-antagonists are capable of treating intractable hiccups. In the initial phases of inflammation, the peripheral neurotransmitter histamine is released from inflammatory cells such as mast cells and basophils. It is responsible for smooth muscle cell contraction, gastric acid secretion and vasodilation and this consolidated action may result in the generation of hiccups. The action of adrenaline and noradrenaline can be better explained with respect to their enzymatic activation. Dopamine can be converted to noradrenaline via the enzyme dopamine beta hydroxylase, which in turn can be converted to adrenaline via the enzyme phenyl ethanolamine N-methyltransferase. Noradrenaline being a post ganglionic peripheral neurotransmitter decreases gut motility and despite the lack of clarity, the interplay of these three chemical messengers and their respective inhibitors could be responsible for inhibiting the reflex arc. Another peripheral neurotransmitter, acetylcholine may also have a role as evidence of anti-cholinergic drugs can inhibit the hiccup reflex.

Etiology:

The most common causes of benign hiccups have been attributed to rapid distension of the stomach as a result of over/ rapid eating or gastric irritation due to spicy food, carbonated beverages, alcohol and even smoking. Intractable hiccups may be due to lesions or stimuli to the reflex arc and their facilitatory neurotransmitters which can affect multiple organ systems via the central and peripheral nervous system. Space-occupying lesions that include aneurysms, abscesses, tumours or inflammatory enlargements within the brain rarely manifest as hiccups but may present besides other important neurological symptoms.[23] Continued irritation of the medullary reflex arc which responds to supratentorial inputs most often occur during infarctions and hemorrhagic strokes which results from the repeated excitatory inputs from the higher centres of the brain.[24] Injuries to the medulla oblongata most commonly seen in the vagal nuclei and nucleus tractus solitarius may cause intractable hiccups[25] as in cases of neuromyelitis optica along with common manifestations of nausea, headache and vomiting.[26] Amongst the vast number of peripheral causes,

the gastrointestinal system appears to be the most prominent with evidence of an inter-relationship between hiccups and gastro-oesophageal (GERD). Hiccups have been demonstrated to inhibit oesophageal motility thereby reducing oesophageal sphincter pressure and altering the anatomy of the gastro-oesophageal junction, predisposing an individual to GERD.[27] In more serious cases, persistent hiccups may go undiagnosed in individuals with gastric or pancreatic cancer with metastatic infiltration to the diaphragm. The tumour or dilation of the oesophagus superior to the stenotic lesion is associated with a reflex action as a result of raised intraluminal pressure in the body.

Hiccups may also manifest in various states of anxiety or psychological disorders as well as toxic- metabolic causes that upset ionic and inflammatory mediator balance. Pre-operative sedation, surgical interventions and the use of long-term medications such as steroids, morphine, azithromycin and anti-cancer drugs like cisplatinum may also trigger the reflex arc as described in Table 1. As many as 20% of Parkinsonism patients on dopamine agonists are also frequently affected as the drugs have a high affinity for D3 receptors.[28] Rarer but documented case reports of excess swallowing of blood and debris following dental surgery,[11] intractable hiccups include herpes zoster when there is vagal involvement,[29] mediastinal lymph node sarcoidosis,[30] and may be a manifestation of seizures in infants.[23]

Table 1: Causes of persistent or intractable hiccups [2, 9, 10, 21, 23]

1. Central nervous system	
a. Vascular	Ischaemic or haemorrhagic stroke, arteriovenous malformations, temporal arteritis, aneurysms, systemic lupus erythematosus- related vascular lesions
b. Infection	Encephalitis, meningitis, brain abscess, neurosyphilis, subphrenic abscess
c. Tumours	Neoplasms in the brain and brainstem
d. Trauma	Trauma to the head and brain
e. Inflammation	Neuromyelitis optica, multiple sclerosis, syringomyelia, hydrocephalus
f. Miscellaenous	Seizures, Parkinson's disease
2. Peripheral nervous system (vagal, phrenic and sympathetic nerves)	
a. Ear-nose-throat	Herpes zoster, rhinitis, otitis media, hair or foreign-body irritation of tympanic membrane, pharyngitis, laryngitis, goitre, cysts or tumours of the neck
b. Cardiovascular	Myocardial infarction, pericarditis, thoracic aneurysm
c. Thoracic	Enlarged lymph nodes secondary to an infection or neoplasm, pneumonia, empyema, bronchitis, asthma, pleuritis, aortic aneurysm, mediastinitis, mediastinal tumours, chest trauma, pulmonary embolism, bronchial carcinoma, tuberculosis
d. Gastrointestinal	Aerophagia, oesophageal distention, oesophagitis, oesophageal cancer, hiatus hernia, gastric distention, gastritis, GERD, peptic ulcer disease, gastric carcinoma, gastric volvulus, <i>Helicobacter pylori</i> infection, pancreatitis, pancreatic cancer, abdominal abscesses, abdominal tumours, gall bladder disease, inflammatory bowel disease, hepatitis, bowel obstruction
e. Lower abdomen	Tumours
3. Toxic-metabolic causes	
a. Toxic	Alcohol, herpes zoster, influenza, tuberculosis, malaria
b. Metabolic	Diabetes mellitus, chronic renal failure, hypocalcaemia, hyponatraemia, hypokalemia, hypocapnia, uraemia

4. Procedural causes	
a. Pharmacological	Steroids, benzodiazepines, barbiturates, sulfonamides, opioids, platinum-based chemotherapeutic agents (cisplatin), dopamine agonists
b. Surgical	General anaesthesia, intubation which may stimulate the glottis, neck extension may stretch the phrenic nerve roots during esophageal stent placement, bronchoscopy, tracheostomy, gastric distention, visceral traction, atrial pacing, catheter ablation, central venous catheterization, dental surgery
5. Psychogenic causes	
a. Psychogenic disorders	Anorexia nervosa, schizophrenia
b. Miscellaneous	Stress, anxiety, sleep deprivation, excitement, fear

Investigations:

The course of the afferent and efferent limbs as well as the vague relation of the hiccup centre poses a challenge to diagnose the etiology. As intractable hiccups may be the sole manifestation of an underlying pathology, it is important to narrow out all possibilities from the history, physical examination and use of medication. The physical examination must analyse all lesions pertaining to the regions of the head and neck, thorax, abdomen and nervous system supplemented by lab investigations and radio-diagnostic aids. Laboratory testing is directed toward suspected abnormalities in the following:

- oesophageal manometry and a 24-h pH-impedance reflux study are diagnostic tests for GERD
- Electrolyte imbalance: Hyponatremia can be either the cause as in cases of patients affected with Addison's disease or the effect by drinking water large quantities of water to suppress hiccups; hypokalemia, hypocalcemia, and hyperglycemia
- Renal function tests to detect uremia
- Liver function tests to evaluate hepatitis
- Amylase and lipase levels to evaluate pancreatitis
- White blood cell (WBC) count to assess infections which may need to be supplemented with urine, sputum or cerebrospinal fluid (CSF) analysis.
- Drug screening to evaluate other contributory causes of toxic-metabolic disorders

Imaging modalities that may be useful adjuncts in the confirmatory diagnosis such as:

- Infections restricted to the otolaryngeal pathway may require a thorough assessment by an ENT specialist
- Chest radiography to identify tumors, detect infection, or assess the thoracic aorta
- Fluoroscopy of diaphragmatic movement to confirm the diagnosis if malignancy is suspected or to determine if the diaphragmatic abnormality is unilateral or bilateral before invasive therapy
- Computed tomography(CT) or cone beam computed tomography (CBCT) can identify soft and hard tissue lesions in the region of the head and neck, thoracic and abdominal cavities.
- Magnetic resonance imaging (MRI) can evaluate vascular relations to the afferent limb and injuries to the medulla oblongata. Neurological symptoms may also need to be supplemented by lumbar puncture to arrive at a diagnosis.

Treatment:

Transient hiccups are self limiting and are treatable while in pathological cases, effective treatment involves the exact diagnosis of the lesion. Non-pharmacological methods tend to be convenient, but if hiccups are prolonged greater than two hours it is advisable to use pharmacological interventions. The most practical approach would be to identify and treat the pathology especially if there is systemic involvement. Unfortunately, with the wide number of pharmacological agents being used; there is an obvious lacuna regarding the pathophysiology of the hiccup reflex.

NON PHARMACOLOGICAL MANAGEMENT

Steger broadly classified three major non-pharmacological methods to treat hiccups viz. nasopharyngeal stimulation, vagal stimulation and respiratory maneuvers.[2] Amongst the methods involved in nasopharyngeal stimulation; the inhalation of smelling salts, intranasal application of vinegar and drinking ice cold water are the most common. Vagal stimulatory techniques such as the use of cold compress to the face, carotid massage, induced fright and vomiting can also cure hiccups. Respiratory maneuvers can be performed either by the patient by holding his/her breath, breathing into a paper bag or the use of a CPAP appliance while the Valsalva maneuver is an assisted procedure. The nasopharyngeal and respiratory techniques cause an elevation in the arterial pressure of CO₂, preventing the progression of hiccups.[32] Yoga and meditation has also been suggested to reduce the risk of hiccups by decreasing anxiety, improving respiration and other cardiovascular parameters.[33,34] Other methods that lack sufficient evidence but have been proposed are the use of acupuncture, hypnosis, meditation, nerve blocks to the afferent limb and C3-C5 region as well as the implantation of a neural stimulating device for the vagus nerve. [2,35] However, these methods are associated with various forms of risk. Acupuncture may result in an increase in acetylcholine esterase which hydrolyzes acetylcholine [36]; however

unsterile needles may cause transmission of blood borne viral diseases while the use of a nerve block or stimulant may cause nerve damage and subsequently affect the organs supplied by them.[2] Hypnosis and meditation may symptomatically treat manifestations of extreme stress, anxiety and fear but fails to address the systemic cause and other associated manifestations. Individuals may tend to go undiagnosed with serious psychogenic disorders like bipolar disorder and schizophrenia that need definite medication and long-term follow up. A false sense of security using alternative medicine may also hamper the progress of an individual, affecting care-takers and supporting members.

Pharmacological management

The most commonly administered drugs to treat intractable hiccups are dopamine and GABA antagonists. Chlorpromazine was the most frequently used pharmacological agent administered as a single IM or IV dose of 25-50mg or given orally 25mg 3 times a day. As various neurological side-effects were reported, it is currently not advised as the drug of choice. Similar side-effects were also seen with anti-psychotics like haloperidol and olanzapine and thus were later avoided as well. Olanzapine is a postsynaptic serotonin antagonist while other drugs such as sertraline, a selective serotonin reuptake inhibitor (SSRI) [37] and tandospirone, a 5HTA1 receptor agonist[38] have also been used. A case report of intractable hiccups that was refractory to haloperidol, responded to another anti-psychotic risperidone which acts on the following receptors: 5HT2A, 5HT1A, 5HT1C, 5HT1D, and D2.[39] Currently, drugs such as metoclopramide and baclofen are often used as alternatives. Metoclopramide, an anti-cholinergic and dopamine antagonist may be useful in treating GERD cases as it promotes gastric emptying[11] and reduces the intensity of esophageal contraction, thereby providing symptomatic relief from hiccups. The only noted disadvantage of metoclopramide has been dyskinesia which has been noted in patients using the drug for prolonged periods.[40] Domperidone has been reported to be useful as it does not cross the blood brain barrier, but high doses may attribute to cardiac arrhythmias and is hence not considered a drug of choice. Gabapentin is an analogue of the inhibitory neurotransmitter GABA used in the treatment of epilepsy. Recent evidence suggests that gabapentin could be a safe alternative by blocking calcium channels that reduce the release of neurotransmitters which modulate diaphragmatic activity. It is prescribed as 300mg, thrice daily and is usually indicated when the episodes are more chronic [19] especially in cases with a CNS pathology. Compared to other anti-epileptic agents, there are fewer complaints of sedation and light-headedness. Baclofen, a GABA derivative is notable for its effect on the vagal efferent pathway and has also been used to treat hiccups caused by CNS tumours and chronic renal failure, by prescribing the drug in doses of 5mg three times a day.[31] The neurological effects are milder and cease with the withdrawal of the drug as compared to metoclopramide and chlorpromazine and is therefore suggested to be the drug of choice for intractable hiccups. Among the four receptors for histamine, H2-receptor blockers and proton pump inhibitors (PPIs) like omeprazole can remedy hiccups by decreasing the input from the GIT to the hiccup center.[41] As there is limited evidence supporting PPIs, using them in GERD patients with intractable hiccups might not be advisable.[2] Methylphenidate, a psycho-stimulant is a receptor modulator of dopamine and norepinephrine and has been shown to inhibit hiccups.[42] This may suggest a that a role may exist between norepinephrine and epinephrine in the pathophysiology of hiccups. Becker has suggested the use of the anti-tussive agent benzonatate.[11] Unlike other cough syrups, it is not opioid based and is an ester local anesthetic derived from tetracaine. It is capable of anesthetizing the vagal afferent fibers involved during coughing and hiccups within 20 to 30 minutes of administration. The recommended dose is 100 mg orally, four times a day and must not be chewed to prevent excessive numbness of the mouth and throat. Other pharmacological interventions that have been documented but lack sufficient evidence to be used include benzodiazepines, carvedilol, amitriptyline and amphetamines.[23] Benzodiazepines have a dose-dependent action on the suppression of hiccups where smaller amounts may stimulate hiccups and greater amounts are capable of arresting them. This has been attributed to the restriction of repeated myoclonic contractions of the diaphragm and thus the inhibition of the reflex arc.[43] With the impetus of finding pharmacological agents that exert fewer central and peripheral neural side effects, there has been an increased drive in assessing commonly available herbal extracts. Though the levels of evidence remain extremely limited, literature reviews claim benefits in improving the neurodegenerative effects seen in Parkinson's disease using *Punica granatum* (pomegranate) extract formulations [44] and extreme states of anxiety with *Cardiospermum halicacabum* (balloon plant).[45] Animal studies performed in rats have also shown statistically significant dose-dependent anti-anxiety effects with the use of *Coriandrum sativum* (coriander or cilantro) when compared to diazepam.[46] Unless there are further experimental studies that support such data, the use of herbal extracts may very much anecdotal and dormant.

Challenges ahead:

The lack of a consensus regarding the pathophysiology and evolutionary mechanism of the hiccup reflex arc has undermined the significance of the persistent and/or intractable hiccups. Incidence rates regarding the different forms of hiccups among various populations with and without systemic pathologies must be emphasized. Unless absolutely debilitating or affecting the quality of life, a patient may not report it as a primary chief complaint. Data regarding patient admissions due to hiccups are inadequate based on the available literature which in turn reflects the paucity of randomised controlled trials with pharmacological and non-pharmacological interventions. Relevant follow-ups must also be given priority in order to assess the levels of evidence between therapeutic modalities that are available and establish guidelines and protocols required for the management of intractable hiccups.

Conclusion:

Hiccups usually result from a multitude of triggering factors involving the reflex arc. In general, hiccups are self limiting in nature and only rarely extend beyond 48 hours. As most symptomatic individuals are treated as out-patients, it is very difficult to estimate the number of cases with intractable hiccups. This underestimation prevents an accurate diagnosis of a serious pathology and therefore, it is imperative to perform a thorough clinical examination and supporting investigations. More importantly, the identified etiology must be managed either pharmacologically or non-pharmacologically or as a combination of the two. Although

multiple treatment modalities have been suggested, the ability to completely cure intractable hiccups remains uncertain and may require further evidence.

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