

## MICROVASCULAR DECOMPRESSION FOR INTRACTABLE SINGULTUS: TECHNICAL CASE REPORT

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**OBJECTIVE:** Intractable singultus is a rare but significantly disruptive clinical phenomenon that often accompanies other diseases but can present in isolation due entirely to intracranial pathology. We report a case of intractable singultus that improved after microvascular decompression and present a comprehensive review of singultus by discussing its similarity to other cases of microvascular decompression, its history and etiology, and its evolutionary basis.

**CLINICAL PRESENTATION:** The patient exhibited intractable singultus for 15 years, resistant to multiple medical regimens.

**INTERVENTION:** Microvascular decompression to relieve pressure on the tenth cranial nerve and medulla oblongata resulted in near total resolution of the singultus.

**CONCLUSION:** Neurovascular compression should be considered a potentially reversible cause of intractable singultus, a significantly disabling clinical phenomenon.

**KEY WORDS:** Cranial nerve X, Intractable singultus, Medulla, Microvascular decompression, Posterior inferior cerebellar artery, Singultus, Vertebral artery.

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Singultus occurs when the diaphragm and intercostal muscles repeatedly and involuntarily contract spasmodically, resulting in inspiration that is abruptly interrupted by closure of the glottis, which causes the characteristic sound. The term “hiccup” derives from the sound of the event, originating from the Latin terminology *singult*, “the act of catching one’s breath while sobbing.” Although generally a self-limiting phenomenon, occasionally singultus becomes intractable and significantly affects quality of life by causing exhaustion, lack of sleep, and weight loss. Singultus that lasts longer than 48 hours is considered persistent singultus; intractable singultus lasts over a month (59).

Although the origin of singultus has engaged the attention of both philosophers and physicians since the time of Hippocrates and Celsus, the exact cause remains a mystery. It is generally believed that singultus serves no known physiological function at this point in human evolution (35); after reviewing 192 references, Launois et al. concluded that “the purpose of the hiccup is unknown” (52). However, it is known that babies in utero hiccup (45) and that singultus is particularly common in premature babies (52). Historically, given that two thirds of

patients with intractable singultus have gastroesophageal reflux, gastrointestinal diseases have been the most frequent causes to search for when making a medical diagnosis (52). Early studies suggested that singultus was not governed by the same centers that controlled inspiration and expiration, but was “gastrointestinal rather than respiratory in nature” (24). Shortt in 1833 first recognized an association between hiccups and phrenic nerve irritation, and Bailey in 1943 proposed the existence of a “hiccup center” located in the upper cervical spinal cord (48).

Intractable singultus affects male subjects more frequently than females; a retrospective study conducted by the Mayo clinic (96) reported 81% of patients (n = 220) with singultus were males. A more recent study reported a higher incidence of singultus in male patients; over a 5-year period of admissions to a single hospital, 54 people were admitted with singultus, with men accounting for 91% of these admissions (22). When considering the overall prevalence of singultus, it is estimated that seven people will present with intractable singultus each year in the setting of a large tertiary care facility (32).

Persistent and intractable singultus may indicate an organic disorder that should be investigated based on history, physical examination, imaging and labs. The treatment is based on the organic disorder, if it is found; otherwise, several nonspecific modalities of treatment are available. Here we present the case of intractable singultus caused by medullary and tenth nerve compression secondary to abnormal neurovascular contact that was significantly improved after microvascular decompression. We also examine other modalities of treatment, pharmacologic and nonpharmacologic; review the literature with regard to medullary lesions that may result in singultus; discuss other etiology of singultus; and explore the evolutionary basis for the existence of singultus.

## CASE REPORT

### History and Examination

The patient, a slim, 41-year-old, right-handed man, presented to our neurosurgery clinic with a 15-year history of intractable singultus. His singultus was almost constant, and he denied a period of time greater than one day during which he did not have singultus. The singultus was stimulated by eating, but it occurred even without prior food intake. It could sometimes be stopped by self-induced vomiting. The patient also suffered from insomnia (his spouse revealed the singultus continued nocturnally) and shortness of breath secondary to the frequency of his singultus. The singultus had severely impaired his functionality, as he had not been able to maintain employment for 3 years and was divorcing from his wife. He had suffered 15 pounds of weight loss due to the singultus and vomiting. He had had limited success with baclofen (Upsher-Smith Laboratories, Inc., Maple Grove, MN), chlorpromazine (Thorazine; Sandoz, Inc., Princeton, NJ), metoclopramide (Reglan; ESI Lederle Generics, Cherry Hill, NJ), and lansoprazole (Prevacid; TAP Pharmaceuticals, Inc., Lake Forest, IL). Extensive gastrointestinal workup by a specialist failed to reveal the cause of his singultus. Gastric emptying study revealed normal gastric and esophageal emptying. Chest and abdomen computed tomography (CT) imaging revealed only gastroesophageal wall thickening. Esophagogastroduodenoscopy revealed diffuse gastritis, which was biopsied and found to have normal histology. *H. Pylori* serology was positive. Otherwise, the patient had noncontributory past medical and surgical history and review of systems. On examination he had no neurological deficits. Specifically, cranial nerve testing was entirely normal.

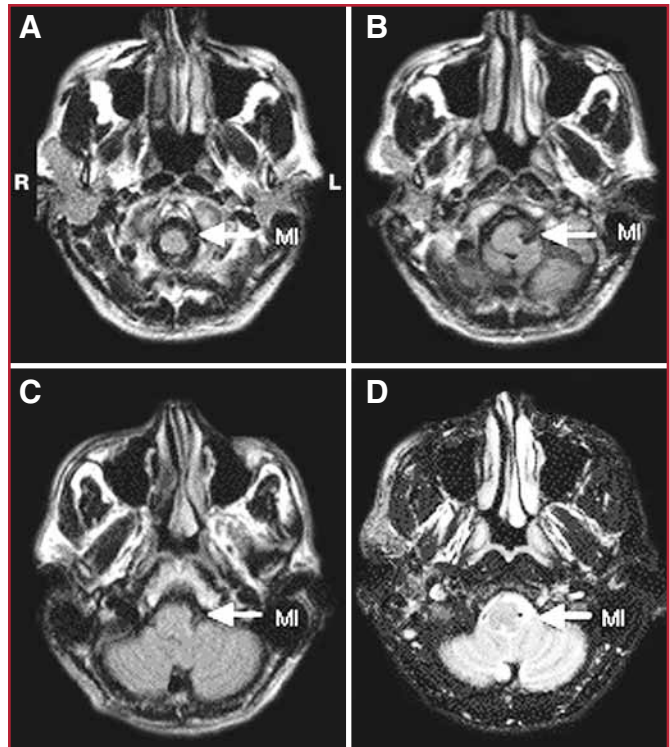
### Imaging

Noncontrast magnetic resonance imaging of the brain was obtained with standard sequences. Axial T1-weighted (Fig. 1A–C) and T2-weighted (Fig. 1D) images demonstrated indentation on the left lateral medulla. A vascular signal void is seen in the depth of this indentation. No other extra- or intra-axial lesions were demonstrated. This indentation was in the lower medulla, near the Xth cranial nerve entry zone (Fig. 1).

### Operation

Given the severity of symptoms and the failure of medical management, we reviewed the radiographic findings with the patient and offered him surgical intervention. He consented to the operation given the severe life impact and disability he was suffering.

The patient underwent left microvascular decompression. A left paramedian suboccipital craniectomy was performed lateral to the foramen magnum, and the dura was incised over the cervicomedullary junc-



**FIGURE 1.** Magnetic resonance images of the brain. **A–C**, axial T1-weighted magnetic resonance images demonstrating the rostral progression of the vertebral artery indentation of the left lateral medulla: slight (**A**), most distinct in (**B**), and fading away (**C**). **D**, T2-weighted image showing the medullar indentation. R, right; L, left; arrow, vertebral artery indentation site, or medullar indentation (MI).

tion. A large vertebral artery was noted to be compressing the medulla and causing indentation. The medulla was decompressed using pledgets of Teflon (Stryker, Roseville, CA) to separate the vertebral artery from the medulla. Several loops of the posterior inferior cerebellar artery (PICA) were found to reside between Cranial Nerves X and XI, pressing on the entry zone of the Xth cranial nerve. The vessels were mobilized, and a pledget of Teflon was placed in between the nerve entry zone and the offending vessels. Fibrin glue was used to maintain the vertebral artery and PICA in a position away from neural elements.

### Postoperative Course

Immediately after surgery, the patient had no singultus. On postoperative Day 2, his singultus returned for a self-limited 4-hour stretch, possibly related to edema. It remained abated for the remainder of his hospital course. By 18 days postoperatively, the patient had gained 6 pounds, as his vomiting had significantly improved. At 5 years postoperatively, he experienced singultus for only one or two 20-minute episodes one or two days a week, and overall remained significantly improved.

## DISCUSSION

Many common situations and several disease states are associated with singultus. Although singultus can develop ran-

domly, it can be related to stomach overdistension due to excess alcohol consumption, a sudden change in stomach temperature such as from drinking a hot beverage and then a cold beverage, emotional excitement, consuming food quickly, laughing vigorously, coughing, or sobbing (53). Decreased kidney function (acidotic state), hyperventilation, anesthesia and anatomic pressure on the vagus or phrenic nerves can also cause singultus (7, 33, 43, 80). Reflux esophagitis partially accounts for over 50% of singultus cases lasting over 48 hours (15, 57, 91). Cyclophosphamide infusion (38), digitalis intoxication (57), myocardial infarction (57), pregnancy (70), and chemotherapy (34, 100) have also been associated with chronic singultus. Abdominal inflammation or hemorrhage (44), subdiaphragmatic abscess (67), abdominal tumors (37), mass lesions of the neck or thorax (1, 64), pneumonia (14), diaphragmatic tumors (13, 63), esophageal dysfunction (86), central nervous system trauma (4, 9), and uremia (49, 75) are other causes (Table 1).

The association of intractable singultus and brain stem lesions has been well described in the literature (Table 2) (2, 3). Studies have reported a connection between intractable singultus and medullary lesions (18, 28, 68, 94), including cases of chronic-stage multiple sclerosis with an enhancing medullary lesion (Table 2) (27, 107). Intractable singultus has also been

associated with periaqueductal lesions in neuromyelitis optica (66), Arnold Chiari Type I malformation (56, 92), and cavernous angioma in the medulla oblongata (71). Medial medullary infarction and hemorrhage have also been associated with intractable singultus, implicating deep tracts in the medulla oblongata to be involved in the hiccup reflex (79, 109).

### Intractable Singultus Reflex Arc

Microvascular decompression has been used successfully to treat trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia for years. Many years ago it was discovered that the neurovascular compression of certain entry zones into the brainstem can lead to these syndromes (19, 30, 62). Our case further substantiates the brainstem as the site of neurovascular compression syndromes for intractable singultus and illustrates the utility of using microvascular decompression to eliminate dysfunctional neurovascular contact responsible for intractable singultus. Figure 2 illustrates the four different types of neurovascular compression syndrome, including our case, in which compression of the medulla by the vertebral artery and of Cranial Nerve X by the PICA were discovered as causes of intractable singultus. The literature additionally reveals two case reports describing neural compression by vascular elements as the presumed cause of intractable singultus. One 70-year-old man presented with a 12-year history of intractable singultus; magnetic resonance imaging revealed dolichoectasia of the right vertebral artery with compression of the brainstem at the pontomedullary junction (104). Johnson (43) first reported microvascular decompression of the vagus nerve for the treatment of intractable singultus. He describes a technique similar to the one we employed, in which a Teflon pledget is placed to eliminate neurovascular contact between the vagus nerve and the PICA. Two additional case reports describe resolution of intractable singultus after resection of cerebellar hemangioblastomas that had been causing compression of the medulla oblongata (72, 93). Similarly, our case illustrates that microvascular compression of the medulla and the Xth cranial nerve can cause intractable singultus. This finding demonstrates the contribution of these neural structures to the reflex arc (Fig. 3) perpetuating intractable singultus, and the utility of performing microvascular decompression as an effective treatment modality for intractable singultus.

Studies of electrical stimulation in medulla oblongata of cats demonstrated hiccup-like responses are generated in the medullary reticular formation lateral to the nucleus ambiguus (8, 81). As evidenced by the many lesions described above, singultus can result from many conditions that affect the supraspinal hiccup center or that stimulate or disinhibit the limbs of its reflex arc. Afferent pathways of the hiccup reflex arc consist of the pharyngeal plexus, the thoracic sympathetic chain T6-T12, the vagus nerve, and the phrenic nerve. The principle efferent limb and diaphragmatic spasms are mediated by motor fibers of the phrenic nerve and vagal nerve (76). Hassler (36) describes singultus as a subcortical equivalent of myoclonus generated at the pontomedullary level, involving the inferior olive, dentate nucleus, and red nucleus. Other authors have developed the concept of denervation supersensitivity

**TABLE 1. Main causes of singultus**

Causes of singultus	Study authors
Esophageal dyskinesia	Cabane et al., 1992 (15)
Cyclophosphamide infusion	Ifran et al., 2004 (38)
Digitalis intoxication	Marai and Levi, 2003 (57)
Myocardial infarction	Marai and Levi, 2003 (57)
pregnancy	Morris et al., 2003 (70)
Chemotherapy treatment	Takiguchi et al., 2002 (100); Gold et al., 1999 (34)
Abdominal inflammation or hemorrhage	Johnson et al., 1983 (44)
Abdominal tumor	Hernandez et al., 1999 (37)
Esophageal dysfunction	Pooran et al., 2006 (86)
Thoracic or abdominal lesions	Mimenza-Alvarado et al., 2002 (64); Aizawa et al., 1992 (1)
pneumonia	Burdette and Marinella, 2004 (14)
Diaphragmatic tumors	Burcharth and Agger, 1974 (13); Michálek and Kautznerová, 2002 (63)
Subdiaphragmatic abscess	Moon, 1974 (67)
uremia	Krahn and Penner, 1994 (49); Neto et al., 2003 (75)
CNS trauma	Barbizet and Pierrot-Deseilligny, 1965 (9); Alderfer and Arciniegas, 2006 (4)

**TABLE 2. Association of brainstem lesions with singultus<sup>a</sup>**

Possible cause of singultus	Study authors	Patient gender, age (yr)	Treatment	Duration of singultus
Chronic stage multiple sclerosis with enlarged medullary lesion	Witoonpanich et al., 2004 (107) de Seze et al., 2006 (27)	female, 32	Intravenous steroids	1 mo
		female, 14	gabapentin,	6 wk
		male, 25	citalopram,	6 wk
		female, 36	amitriptylline	6 wk
		male, 25		2 yr
Medullary lesions	Shibazaki et al., 2006 (94) Chang et al., 1993 (18)	female, 61	methylprednisolone	N/A
		male, 50	heparinization	2 wk
		female, 62	chloropromazine	1 mo
		male, 66	and metoclopramide,	3 wk
		male, 38	chloropromazine	3 wk
		male, 39	hydrochloride and metoclopramide, carbamezapine and metoclopramide, tumor removal	N/A
Medial medullary infarction and hemorrhage	Yoshii et al., 1996 (109) Okada et al., 2007 (79)	male, 54	Antiedema agents and thromboxane synthetase; N/A	2 wk
		male, 52		N/A
Medullary infarct and right Cranial Nerve X, 11, and 12 palsies	Delèvaux et al., 2005 (28)	male, 44	Coricosteroids and low dose aspirin	3 wk
Periaqueductal lesions in neuromyelitis optica	Misu et al., 2005 (66)	female (n = 5), 20–70	methylprednisolone	2 days–1 mo
Cavernous angioma of the medulla oblongata	Musumeci et al., 2000 (71)	Male, 46	angioma resection	2 mo
Brainstem infarction	al Deeb et al., 1991 (2)	male, 65	clonazepam	5 mo
Tuberculomas at the cervicomedullary junction	al Deeb et al., 1991 (2)	male, 55	antituberculous	4 mo
		male, 24	chemotherapy	3 wk
Vermian tuberculoma	al Deeb et al., 1991 (2)	male, 45	antituberculous chemotherapy	7 yr
Cerebellar hemangioblastomas	Nagayama et al., 2004 (72) Seyama et al., 2001 (93)	female, 52	hemangioblastoma resection	2 yr
		male, 38		8 wk
Arnold Chiari Type malformation Syringobulbia in dorsal medulla and a large cervical syrinx C2-C7; Arnold Chiari Type I malformation with large cervicothoracic syringomyelia	Seki et al., 2004 (92) Loft and Ward, 1992 (56)	male,	foramen magnum decompression	2 wk
		27 yr		6 mo
		male, 19	ventriculoperitoneal shunting	

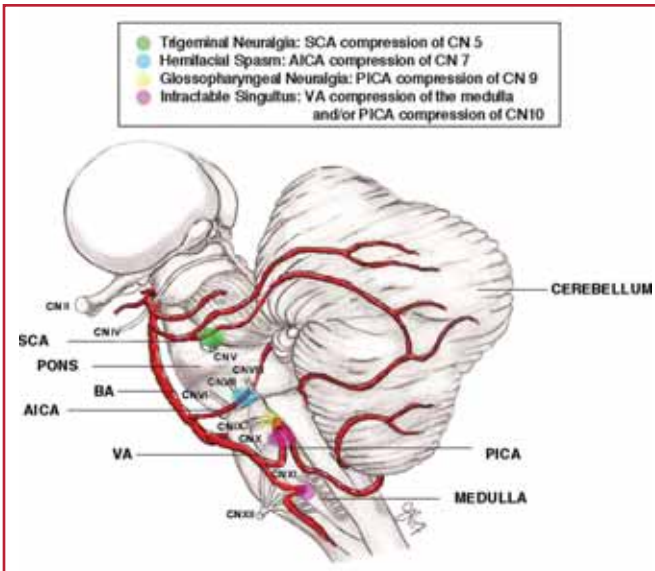
<sup>a</sup> NA, not available.

caused by a lesion-induced dysfunction of the inferior olivary complex, nucleus ambiguus, and adjacent medullary reticular formation (46, 51, 61, 101). Similarly, al Deeb et al. (2) and de la Fuente-Fernandez (25) hypothesized that the anatomic network involved in hiccup activation includes the inspiratory dorsal group of the nucleus tractus solitarius and the ventral group of the nucleus ambiguus, relaying the Hering-Breuer reflex inhibiting continued inspiration (2, 25). Moreover, they proposed that both groups are under the control of the pontine pneumotaxic center, which curtails inspiration, and the apneustic center, which cancels the activity of the pneumotaxic center. Voluntary supranuclear control is mediated by descending corticobulbar pathways. Intractable hiccup may be consid-

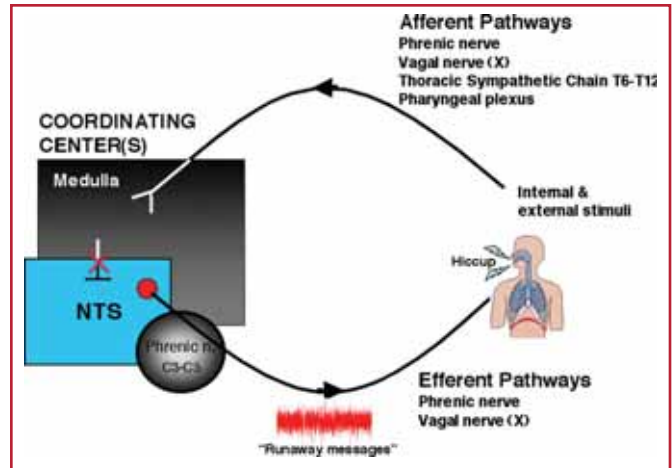
ered akin to a myoclonic jerk due to disruption of supranuclear and ventral ambiguous regulatory control. Brainstem lesions involving descending corticopontine or corticomedullary fibers will release the dorsal group of the nucleus tractus solitarius from regulatory control and enable autonomous myoclonic discharge of the solitary nucleus (Fig. 3) (2, 3).

**Nonsurgical Management of Singultus**

The vast majority of hiccup episodes does not require surgical management and can be often curtailed by stimulating the uvula or pharynx or disrupting diaphragmatic rhythm. Home remedies include distraction and being startled; consumption of sweet or sour foods; psychosomatic measures including



**FIGURE 2.** Five brainstem sites of four neurovascular compression syndromes, including our case of intractable singultus. Green, SCA compression of CN V root entry zone, resulting in trigeminal neuralgia; blue, AICA compression of CN VII, resulting in hemifacial spasm; yellow, PICA compression of CN IX, resulting in glossopharyngeal neuralgia; pink, VA compression of the medulla or PICA compression of CN X, resulting in intractable singultus. SCA, superior cerebellar artery, VA, vertebral artery; PICA, posterior inferior cerebellar artery, BA, basilar artery; PCA, posterior cerebral artery; AICA, anterior inferior cerebellar artery; CN, cranial nerve.



**FIGURE 3.** Basic mechanism of the hypothetical reflex arc for intractable singultus. Basic mechanism of the hypothetical reflex arc for singultus depicting medullary dysfunction as a main contributing neural source of intractable hiccups. The singultus or hiccup reflex arc comprises three basic components: afferent pathways, coordinating centers, and efferent pathways. Afferent inputs consist of vagus and phrenic nerves, the thoracic sympathetic chain T6–T12, the pharyngeal plexus, and others, such as the peritoneum viscera, stomach, esophagus, diaphragm, ear, and nose. Internal and external stimuli such as food and fluid intake, temperature change, and emotional effects can influence afferent pathways to the coordinating center(s) regulating the hiccup reflex. The hiccup center(s) are located in the brain stem, the medulla being one of the main components of these coordinating centers. Although not shown, in addition to corticomedullary regulation, corticopontine, nucleus ambiguus, and inferior olive contribute to regulate the hiccup reflex. Descending brainstem fibers exert inhibitory regulatory control over the nucleus tractus solitarius. Therefore, microvascular compression of the medulla or lesions of the brainstem “irritate” or disrupt inhibitory control of the nucleus tractus solitarius, thereby permitting the nucleus tractus solitarius to exhibit autonomous myoclonic discharge. As a result, these “runaway messages” descend along efferent pathways such as phrenic and vagal nerves to produce intractable singultus. The inspiratory centers of the cervical spinal cord (C3–C5 cell bodies located in the ventral horn) give rise to axons composing the phrenic nerve. NTS, nucleus tractus solitarius.

relaxation; various swallowing and eating techniques felt to remove irritants or reset mechanisms in the affected region; complete exhalation; holding one’s breath while swallowing water or saliva; smoking; sneezing; altering breathing patterns; and, in babies, eliciting the sucking reflex. Breathing into a bag to induce respiratory acidosis produces vasodilation and depression of the central nervous system. Blood flow increases to the affected muscles, and aberrant nerve impulses are believed to be suppressed (47).

Nonpharmacologic means for treating singultus include psychological therapy (10, 89), vagal maneuvers (84), acupuncture (108), irradiation of acupoints (17), and cervical epidural block (90). Digital rectal massage has been also described as an effective treatment in stopping singultus by stimulating the vagus nerve, thereby blocking “runaway messages” (Fig. 3) on the vagus nerve (31, 77–78).

This case report further substantiates that patients with intractable singultus should be examined for an underlying disorder while being treated symptomatically. Chest, upper abdomen, and brain imaging should be used to rule out anatomic etiologies, while a number of pharmacological agents can be explored simultaneously as effective treatment modalities. A vast number of pharmacological agents is used to treat singultus, including gastrointestinal stimulants, intravenous steroids, antipsychotic and anticonvulsant medications (4, 11,

12, 20, 21, 23, 26, 32, 37, 39–41, 42, 50, 54, 55, 57, 58, 60, 65, 69, 73, 74, 79, 82, 83, 85, 87, 88, 95, 98, 99, 102, 103, 106). Anticonvulsants such as gabapentin (5, 68) may effective, because singultus is considered to be a form of myoclonus caused by repeated and abnormal activity of the solitary inspiratory nucleus due to release of higher nervous system regulatory control (2, 3, 68).

Even when singultus persists despite medical therapy, surgical intervention is rarely pursued. However, patients with disabling singultus in whom medical management fails may be considered for phrenic nerve stimulation (6, 29) or blockade or ablation (16, 43, 55, 63). Phrenic nerve surgery for singultus has been reported since 1931 (105). Vagal nerve stimulation has been reported to resolve singultus that began after a posterior fossa stroke (84).

## Evolutionary Basis for Singultus

Although singultus has limited or no utility in modern human beings, the reflex may have been helpful to our quadruped and marine ancestors, whose esophagi ran perpendicular to the force of gravity, in aiding peristalsis that had been ineffective in mobilizing dislodged food stuck in the esophagus (45). Such dislodged pieces may apply pressure on the phrenic nerve and activate the hiccup reflex, contracting the diaphragm and creating a pressure differential, with highest pressure near the mouth and low, vacuum-like pressure in the chest, to assist peristalsis (45). Some have proposed that the hiccup reflex is evolutionarily related to amphibian respiration, whereby air and water are taken in by a motor reflex (97). According to Straus et al. (97), the hiccup is an evolutionary antecedent to advanced lung respiration, since its motor pathways form prior to those enabling normal lung ventilation, and both singultus and amphibian gulping are inhibited by elevated CO<sub>2</sub> and by the centrally acting muscle relaxant, Baclofen, demonstrating parallel physiology. A study by Kahrilas (45) has suggested that the retained utility of singultus in humans resides during neonatal development. Ultrasound has revealed that babies in utero hiccup, perhaps as an exercise for the respiratory system prior to birth or to prevent amniotic fluid from entering the lungs. These theories may explain why premature neonates spend 2.5% of their time hiccupping; their premature respiratory development at this stage may result in behavior resembling amphibian gulping.

An American named Charles Osborne had singultus for 68 years, from 1922 to 1990, and was entered in the *Guinness World Records* (<http://www.guinnessworldrecords.com>) as the man with the Longest Attack of Singultus.

## CONCLUSIONS

Intractable singultus can be a seriously disabling condition with many potential causes. Because neurological examination is often normal, the diagnosis of nerve compression can easily be missed. After common causes are ruled out, microvascular decompression may be considered for appropriate candidates who have failed medical management.

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## COMMENTS

The authors have described the highly unusual and very interesting case of a patient who exhibited intractable singultus for 15 years and underwent microvascular decompression of the vagus nerve and medulla with an excellent clinical response. The authors have provided an authoritative review of the subject, describing a number of patients with chronic singultus associated with brainstem lesions primarily

affecting the medulla. Only two cases of microvascular decompression for intractable singultus have been described in the past, along with two additional reports of resolution of singultus after resection of cerebellar hemangioblastomas.

The primary strength of this article is the exhaustive review of the subject, including a description of the reflex arc involved in singultus and a review of the various therapeutic options, including microvascular decompression, for addressing this devastating condition.

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Intractable singultus is an unusual condition, but when it occurs, it is extremely debilitating. In this article, Farin et al. describe their experience with a patient who underwent microvascular decompression of the Xth cranial nerve at the junction with the medulla, who had almost total resolution of his symptoms after a microvascular decompression. In their very complete discussion, the authors describe the reflexes that are responsible for this clinical syndrome and speculate on mechanisms whereby it may occur. This very complete case report and the literature review are informative.

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The authors report a patient with intractable singultus, or hiccup, that improved after microvascular decompression. The magnetic resonance imaging scan demonstrated indentation on the left lateral medulla, and a vascular signal void was seen in the depth of this indentation. During the operation, a large vertebral artery was noted to be compressing the medulla and causing indentation. In addition, several loops of the posterior inferior cerebellar artery were found to reside between Cranial Nerves X and XI, pressing on the entry zone of the Xth nerve. The microvascular decompression provided partial but very significant relief to the patient.

Although extremely rare, intractable singultus is one of the possible microvascular compression syndromes and needs to be recognized by the neurosurgical community. This article provides an accurate illustration and comprehensive review of this exceptional entity.

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