Opinion: Uncovering diaphragm cramp in SIDS and other sudden unexpected deaths

Companion Guide

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In brief:

Compared to the other vital pump, the heart, the diaphragm is grossly understudied and under-appreciated. This paper delves into the long-standing mystery of Sudden Infant Death Syndrome (SIDS) and its potential underlying mechanisms. The authors present a novel hypothesis centered around a newly recognized condition termed diaphragm cramp-contracture (DCC), which they suggest could be a significant factor in spontaneous respiratory arrests in infants and children. Drawing from an extensive literature review and the unique case of a patient with a remarkable medical history, DCC may elucidate some of the unexplained phenomena associated with SIDS.

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Introduction

The mystery behind sudden infant death syndrome (SIDS, or cot death) is unravelling. In a sentence: based on over two years of extensive literature reviews stemming from a patient with an extraordinary medical history, **we have uncovered a previously unrecognized cause of spontaneous respiratory arrests in children that appears to be an elusive SIDS mechanism: novel (new) diaphragm cramp-contracture (DCC)**. This plain English bullet-point list of essential findings raised in the above-titled Opinion paper is slimmed down and geared for all readers (including lay persons, researchers and fellow physicians). Only the most pertinent research papers are cited (*with clickable links* [#]). Hypotheses have grey backgrounds whereas SIDS prevention advice is in yellow. It must be noted that DCC has not been validated yet in lab.

- SIDS has probably plagued humankind for as long as *Homo sapiens* have existed: a 300,000-year-old mystery.
- Approximately 8-10 children are found lifeless each day in Canada and the USA, combined, from SIDS and sudden unexplained deaths in childhood, or SUDC (or 8.4 per 10,000 live births, from 2001-2019). The devastating losses, lifelong grief and unrelenting parental self-blame need no further discussion. Grieving families deserve a better explanation than what is currently offered.
- There are three leading SIDS hypotheses: **(1)** Triple-Risk (*Filiano & Kinney* 1994), **(2)** Infection-based (*Paul Goldwater* 2003) [1] and **(3)** Critical Diaphragm Failure (*Siren & Siren* 2011) [2]. DCC incorporates all three, with particular emphasis on the latter. In fact, the *Siren* article helped set the groundwork for this paper.
- **Inexplicably, unlike the heart (the other vital pump), the respiratory diaphragm has been grossly understudied and unappreciated as causing serious presentations, including sudden deaths**. It is often neglected when considering the causes of brief resolved unexplained events in children as well as (1) respiratory conditions (e.g. apneas and "breath-holding" spells, hypo- and hyperventilations, rib retractions, periodic and paradoxical breathing, oxygen desaturations and high CO_2 levels, and even rapid breathing itself), (2) neurological symptoms (hypotonia, syncope, visceral aura and being a cause *and effect* of some seizures) and (3) cardiovascular disorders (hypotension, bradycardia, new murmurs, pulmonary hypertension, sudden cardiac deaths). **Part of the problem is that the diaphragm hides from plain sight and pathological contractions are difficult to separate from normal ones. Also, diaphragm histology is not being routinely checked** and despite some abnormalities reported in sudden unexpected deaths, might be inadvertently written off as artifacts. Lastly, like the God-of-the-gaps principle, central nervous system pathology might have received too much credit explaining things like central and mixed apneas, hypoxic ventilatory depression, autonomic seizures, or cerebral edema as a terminal cause of death in ketoacidosis [along with an acidosis-lowered threshold for arrhythmias of the heart (and diaphragm!)]. *Lopes et al.* (1981) put it best, "The neural basis for apnea is so deeply entrenched that it is difficult to accept that some apnea may be due to respiratory muscle failure".
- This dome-shaped skeletal muscle, physically separating the chest (thoracic) and abdominal cavities, is the primary inspiratory muscle (see Video S1 for animated anatomy). Inspiratory "neural" signals from the central nervous system (CNS), the brain, are carried by the left and right (bilateral) phrenic nerves, causing the diaphragm to contract bilaterally in inhalation (inspiration).

As it descends towards the abdomen, the increasing chest volume (and lower pressure) creates an intrathoracic vacuum, expanding the lungs with air. When the diaphragm relaxes, exhalation (expiration) occurs passively, until a point in time called "end-expiration", when the breathing cycle restarts.

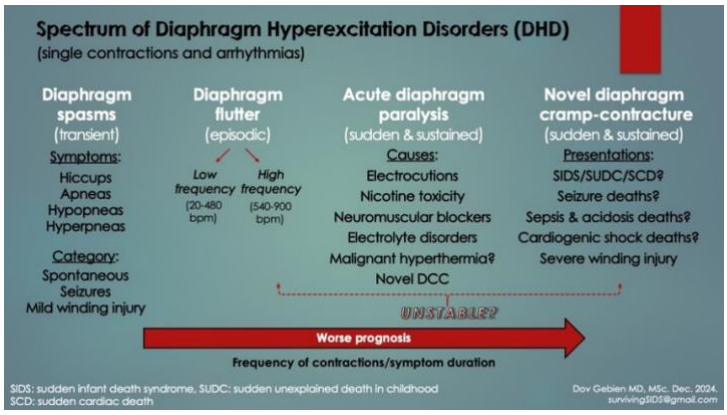
- New information presented here stems from a solitary patient, "Patient 0", representing a sample size of only one (N=1). Medical breakthroughs do not normally happen this way, however, was the case with penicillin's antibacterial effect.
- The story is not fictitious. The ideas and evidence derived from the patient's consistent and reliable account are compelling.
- Based on this healthy 53-year-old male who disclosed spontaneous life-threatening cramp-like **"bearhug pain apneas"** awakening him from sleep sporadically from ages 7 to 17, using logical (clinical) reasoning, we arrived at the diagnosis of **diaphragm and intercostal muscle cramps**. Making a firm diagnosis without confirmatory testing was also unusual.
- The unique combination of bilateral rib bearhug pain with inspiratory arrest apnea and gasping (his mouth had opened involuntarily, unable to inspire) made it straightforward excluding other causes because they did not feature both symptoms nor were they spontaneous and recurrent (see Table S1: *Differential Diagnoses*). Furthermore, because he could not inspire *despite trying*, it appears there was a total airway obstruction. Additional details of his extraordinary story are given in the *Patient's Perspective*.
- Diaphragm cramp (but not spasm) was medically unheard prior to our report. Perhaps because of mortality bias, where victims do not live to talk about it (let alone being recruited into research studies). Also, DCC is thought to affect infants and preverbal children most commonly; too young to remember. Lastly, rapid eye movement (REM) sleep is involved, the deepest sleep stage, making memory recall vague. For further speculation, see Table S2: *Why DCC is Unknown to Medicine*.
- Despite the duress of severe pain and imminent death, the 7-year-old Patient 0 had the presence of mind to experiment. Incredulously, he discovered symptoms could be aborted by essentially breathing out to breathe in: an expiration followed immediately by three short burst, pursed-lip inhalations (see Video S2 for his autoresuscitative *Rescue Breath Technique*). With subsequent DCC events, he reused the same technique. However, he eventually recognized that painful twitches in his ribs (fasciculations) during sleep always preceded the full intensity bearhug cramp. If he quickly inspired *before reaching end-expiration*, the bearhug could be avoided. Lastly, given he learned to do this in his sleep suggests he had endured numerous DCC events over his childhood and youth.
- The fact that a 7-year-old child was able to keep calm, troubleshoot and then devise an impromptu counterintuitive solution *while unable to breathe* and *alone in bed,* is remarkable. It is considered that he would have perished if not for the rescue breaths. [Perhaps by recoiling first, this had forced the diaphragm out of its hypercontracted, incapacitated state (inspiration achieved by rapid expiration-inspiration)].

- Had he not autoresuscitated, critically low blood oxygen levels would have ensued (hypoxemia), leading to a rapid loss of consciousness (syncope, within 5-10 s), cardiac arrest (1-2 min later) and death (in another 5 min), for a total duration of only 10 min post-apnea. Brain injury would have started within 3 minutes of apnea.
- Had Patient 0 perished, the diagnosis of "sudden unexplained death in childhood" (SUDC) would have applied given he was over one year of age. Under 1 year old (infancy), it would have been "sudden unexpected death in infants" (SUDI), which includes sudden infant death syndrome (SIDS). SIDS is defined as the sudden death of an infant which remains unexplained after thorough investigation including a complete autopsy, death scene investigation and detailed clinical and pathological review [1]. SIDS is 40 times more common than SUDC and there is no evidence suggesting different causes. In fact, if they do share a common mechanism, it would suggest a developmental vulnerability becomes outgrown, most likely from a CNS, cardiac or respiratory cause. The latter includes the lungs and respiratory muscles but has received the least research attention.
    - Low birth weight, preterm (premature) and younger full-term infants (under 4 months) are most vulnerable to respiratory muscle fatigue and failure [3]. Incompletely developed respiratory muscles and higher workloads are primarily responsible.
- Despite not being an infant at the time, overall features of Patient 0's apparent life-threatening events (ALTE) shared similarities with those of SIDS. For instance, his death would have occurred *silently* and *rapidly* during *sleep*, and the preceding respiratory arrest had a *sudden, unexpected and spontaneous onset* with *no preceding respiratory distress*. Also, he shared many risk factors with SIDS: male predominance, history of night sweats (overheating), prone sleeping position (face down), pulling loose blankets over shoulders or head (rebreathing), smoking household and a colder geographic climate.
- SIDS research has long suggested a respiratory cause. One involving airway obstruction:
    - In nine preterms aged 1-6 months who had basic home cardiorespiratory recordings of their final moments, seven had terminal apnea, gasping and evidence of airway obstruction just before death (*Poets et al.* 1999) [4]. Symptoms identical to Patient 0's.
    - Respiratory observations in future SIDS victims compared to healthy babies revealed more sleep-related apneas, as well as apneas and intermittent airway obstructions while bottle feeding (not related to coughing or choking) [5]. In another study confirming the first, the obstructed breaths occurred mainly during REM sleep (78% of events), were accompanied by drops of heart rate (bradycardia) and oxygen saturation levels down to 75% (hypoxemia) and associated with profuse night sweats while sleeping [6].
    - Autopsy evidence: intrathoracic point-like (dot) hemorrhages (Tardieu petechiae), pulmonary congestion (heavy, fluid-filled lungs) and edema (frothy, blood-tinged airspace fluid) and gastric contents found in the mouth and airways. To produce these findings, a struggle to breathe against airway obstruction (agonal respirations) had likely created extremely negative intrathoracic air pressures, shunting blood into the lungs at elevated pressure (causing pulmonary hypertension and edema), while exposing the stomach to high intraabdominal air pressure.

- Despite intense effort and massive resources poured into SIDS research since the 1990s, the cause of this obstruction has never been found. Research shifted to the CNS, but with disappointing results.

Diaphragm Contraction Abnormalities (Hyperexcitability Disorders)

- With diaphragm cramp in mind, the medical literature surprisingly revealed a wide variety of disorders in all ages, many obscure, featuring involuntary diaphragm contractions. However, hiccups represented a more commonly experienced symptom (from brief diaphragm spasms). Both spontaneous and traumatic forms of excitation existed. Collectively, we categorized them all as "diaphragm hyperexcitation disorders" (**DHD**), as seen in the slide below.



- It is important to note that mortality bias could have prevented us from appreciating the full extent of DHD symptoms, particularly in DCC. If one suddenly perished unwitnessed, the true cause would be missed and the diagnosis classified, again based on age, as SIDS, SUDC or SCD (or sudden unexpected death in epilepsy or traumatic cardiac arrest). Unfortunately, current autopsies do not reveal evidence of DCC because histology is either not being done or the microscopic changes are written off as artifacts.

- The causes of DHD are complex, complicated and beyond the scope of this paper. Associated medical conditions include chronic disorders of the neurological, neuromuscular and respiratory systems, infections [e.g. viruses like COVID, influenza and respiratory syncytial virus (RSV)], electrolyte and acid-base disorders, the postpartum state, and not uncommonly, *psychological distress*. Many of these overlap with the causes of diaphragm weakness already mentioned.

- **Diaphragm Spasms** (**DS**): Brief, 1-2 s, *spontaneous* contractions in all ages, primarily preterm babies, that can run in succession sometimes up to 30-60 s at a time, causing worrisome oxygen desaturations. Symptoms may include innocent hiccups and other gastrointestinal symptoms in some individuals, whereas persistent hiccups, forced expirations and apneas-hypopneas (shallow respirations) in others. *Traumatic DS* occurs in abdominal winding injuries (celiac or solar plexus syndrome) where there is a blunt blow to the upper abdomen (epigastrium) or chest, commonly seen in martial arts for example [7]. Like spontaneous DS, a forced expiration may occur followed by an involuntary apnea, inevitably triggering panic because the victim cannot breathe in for a few

seconds. Sometimes, the victim might collapse (syncope) from severe hypoxemia. See *Traumatic DCC* just below for sustained DS, which is thought to have the worst prognosis. [*Skip far ahead to learn more on Winding Injuries*]

- **Diaphragm Flutter** (**DF, van Leeuwenhoek's Disease**): Spontaneous episodic sudden-onset *rhythmic* diaphragm contractions in all ages lasting minutes to hours. Both low and high frequency forms exist: 20-480/min versus 500-900/min, the former similar to cardiac atrial flutter whereas the latter to ventricular fibrillation. Antonie van Leeuwenhoek was the first to describe it in 1723 when he wrote, "I thought I was at death's door. I was seized by a violent movement around that large and vital organ we call the diaphragm, so much indeed that those standing around were not a little alarmed" [8]. He died suddenly later that same year, reportedly from DF. Although symptoms may include bulging epigastric pulsations and epigastric/chest pain, respiratory distress is more common, sometimes with pale skin (pallor) or blue discolouration (cyanosis), requiring assisted breathing (CPAP or mechanical ventilation). DF in infants might be more common than thought. Specialized studies are needed to identify it, such as respiratory inductive plethysmography (RIP) or electromyography (EMG), and symptoms overlap with those of respiratory distress.
- **Respiratory Flutter** (**RF**): Identical to DF, also in all ages, but other respiratory muscles contract simultaneously with the diaphragm, including the intercostal (between-rib), neck (scalene) and abdominal wall (rectus abdominae) muscles. Three newborns with RF were reported to have respiratory distress requiring short-term assisted ventilation (until outgrowing symptoms). The clustering of cases over a short period of time prompted the authors to declare that "RF was an underrecognized cause of respiratory failure in neonates" [9].
- **Diaphragm** and **Respiratory Myoclonus**: Like DS and DF/RF but with bursts of *arrhythmic* diaphragm ± accessory respiratory muscle contractions, sometimes with abdominal muscle pulsations. Epigastric/chest pain and disabling shortness of breath have been reported. More than one paper on the subject mentioned a spectrum of diaphragm contractions.
- **Belly Dancer's Dyskinesia:** Slow contorting, writhing contractions of the rectus abdominae muscles, causing the umbilicus to move slowly in all directions. It remains uncertain, however, if diaphragm contractions accompany these.
- **Acute Diaphragm Paralysis (ADP)** and **putative Diaphragm Cramp-Contracture** (**DCC**): Both cause sustained apneas (respiratory arrests) from sudden inactivation of the diaphragm. Severe hypoxemia rapidly follows, causing secondary cardiac arrest and death if not aborted or resuscitated*. ADP may occur in spinal cord injuries of the neck, electrocutions and seizures (the latter was experimentally induced in mice) as well as with neuromuscular blockers like nicotine, succinylcholine and neurotoxins (e.g. curare, tetanus). Similarly, we proposed *spontaneous* DCC-induced ADP occurs in vulnerable infants and children (leading to SIDS and SUDC, respectively; more below). In addition, that *traumatic* DCC-induced ADP occurs in some high-impact blunt abdominal winding injuries (causing secondary cardiac arrest deaths). Examples include motor vehicle collisions, falls from heights and high-impact bodily collisions.
    - *A near-fatal cardiac arrest occurred in the Damar Hamlin NFL injury (2023), in which Mr. Hamlin collapsed after colliding with another player. On one particular video angle, he

appeared not to have seen the imminent collision and did not brace himself in time. A shockwave could be seen on slow-mo replay traversing his body before he fell. He then stood up trying to remove his helmet but fell backwards and apparently lost consciousness. We believe his diaphragm had absorbed some of the kinetic force of the collision, triggering DCC respiratory arrest. Ensuing rapid hypoxemia could have caused the syncope and secondary cardiac arrest (not primary, as commonly held). Fortunately, CPR was immediately started, and paramedics apparently brought his pulses back [although he may not have actually lost them in the first place]. Despite commotio cordis thought by most to be causal (primary cardiac arrest), that involves a *projectile* hitting the chest and occurring *directly over the heart*, which did not happen.

- Nicotine is a highly potent neuromuscular blocking agent that induces rapid respiratory arrests by peripheral ADP (not CNS induced). Deaths occur within 5-30 min, even from minute ingestions (in one case, a 6-year-old who ate snuffbox scrapings). This is important because tobacco smoke exposure is a SIDS risk factor. Younger children, especially infants, would be most vulnerable.

SIDS Hypothesis: Nicotine absorption from household tobacco smoke in sleeping infants with diaphragm fatigue causes ADP (peripheral) respiratory arrest by reducing the DCC threshold.

Nicotine is exceptionally dangerous in small children, even with minute amounts. It is important to keep vapor liquids safely stored and do not smoke anywhere near an infant or in the household. But if so for some reason, then do not let the child sleep upstairs (smoke rises).

To prevent rebreathing of exhaled gases, use a bedroom fan and slightly ajar window to gently stir the air. No bed companions, loose bed blankets, bed toys or sleeping face-down (prone).

Do not allow the child to sleep on your chest or on the sofa, even for a short nap (SIDS cases have occurred this way).

Breathing Mechanics, Respiratory Weakness and Failure

- The inspiratory muscles include the diaphragm and respiratory accessory muscles (**RAM**) which reduce diaphragm workload in times of need. With inspiration in adults, RAM expand the ribcage whereas in infants, stabilize the plastic cartilaginous chest wall from deformity. Plasticity is a major fatiguing factor in younger infants but fortunately, improves with hardening by ossification.
- External intercostal muscles (**ICM**) are the primary inspiratory RAM. Others include the scalenes and sternocleidomastoids of the neck and pectoralis muscles of the chest (not the abdominal muscles, which assist expiration).
- Normally, the diaphragm-to-RAM contribution to the work of breathing (**WOB**) is about 70:30. However, RAM workload increases under higher physical demand such as exercise, obstructive sleep apnea or respiratory infections (causing airway congestion, wheezing, lung consolidation or small airway collapse or atelectasis).
    - Respiratory infections are categorized as upper airway (**URI**), such as the common cold, laryngitis, pharyngitis or bronchitis; and lower (e.g. pneumonia, viral bronchiolitis). In addition to increased WOB from added airway resistance, the latter two also impair gas exchange in the lungs, further increasing respiratory rate, metabolic demand and WOB.

- Ventilatory workload normally becomes diverted to RAM as diaphragm fatigue sets in (and vice versa). This is known as **respiratory load sharing** (or load dependence). ICM contractions become visible as *rib retractions* (sucking in of the intercostal soft tissues). As they tire (or fail), work is diverted back to the diaphragm (proposed to be the mechanism of *periodic breathing*: cycles of respiratory muscle fatigue and failure worsened by REM sleep ICM inactivation followed by load-dependent compensation). Also, *paradoxical breathing* can develop in severe diaphragm fatigue (possibly from diaphragm arrest). With inspiration, the chest wall contracts instead of expanding while the abdomen moves up and in instead of bulging down and out. This is worrisome because total respiratory failure can ensue suddenly (sustained apnea).

Paradoxical breathing is a medical emergency in infants. Also, although rib retractions on their own may not be a medical emergency, if they occur with rapid breathing, sweating, hiccups or any form of distress, have your child seen by a doctor ASAP.

- The causes (etiologies) of **inspiratory muscle weakness** in all ages determined upon literature review are summarized in **Table 1**. They may occur gradually over a long period of time (chronic) or acutely. Some are irreversible but sometimes may improve with time (e.g. phrenic nerve injuries). Nicotine exposure and electrolyte disorders are known SIDS risk factors.

Multi-organ: CNS, phrenic nerve(s), diaphragm, RAM		Onset	Side	RAM Involved	Citations
Electrocution	Lightning, low- and high-voltage shocks	S	Both	✓	[1,2]
Neurotoxins	Nicotine, botulism, tetanus, curare, organophosphates, carbamates, tetrodotoxin, strychnine, envenomations	S	B	✓	[3-5]
Medications	Neuromuscular blockers, aminoglycosides, catecholamines	S	B	✓	[6-8]
Electrolytes	Hypomagnesemia, hypocalcemia, low and high potassium, hypophosphatemia	S,G	B	✓	[9-12]
Metabolic	Acidosis *(DKA)*, endocrinopathies (*pheochromocytoma crisis), eating disorders*	S,G	B	✓	[13,8,14]
Inflammatory	Vasculitis, pneumonia, pleurisy, herpes zoster, SARS-CoV-2 (COVID-19)	G	B	✓	[15-17]
Neurologic & myopathic	Guillain-Barré syndrome, polio, ALS, myasthenia gravis, Lyme disease, rabies, muscular dystrophy, polymyositis, dermatomyositis, inclusion body myositis	G	B	✓	[18,19,15,16]
Phrenic nerves and nerve roots					
Traumatic	Cervical spinal cord transections or contusions (above C5)	S	Both	✓	[20,21]
	Phrenic nerve injuries (blunt, penetrating, traction, compression)	S	Both	0	[22-24]
Iatrogenic	Birth trauma (asphyxia), chiropractic manipulations	S	Both	0	[25-28]
	Cardiothoracic surgeries, cardiac cryoablation	S	Both	0	[29-31]
Compression	Cervical osteoarthritis, tumours (bronchogenic, mediastinal), aortic aneurysm	G	U	0	[32,15,16]
Diaphragm					
Traumatic	High velocity: contusion, hemorrhage, rupture, paralysis	S	Both	0	[33,34]
	Low velocity: *winding injury* (celiac or solar plexus syndrome)	S	Both	0	[35-37]
Asphyxia	*Restraint cardiac arrests, crush injury, chemical asphyxiants*	S	Both	✓	[38-40]
Exposures	Cold water submersion, heatstroke, conducted electrical devices	S	B	✓	[41-44]
Spontaneous	*Diaphragm cramp-contracture*	S	B	0	[45]

RAM: respiratory accessory muscles, S: sudden, G: gradual, Both: bilateral and unilateral, B: bilateral, U: unilateral, CNS: central nervous system, DKA: diabetic ketoacidosis, ALS: amyotrophic lateral sclerosis, *Italics:* putative (unproven).

Table 1: Causes of inspiratory muscle weakness in all ages. Citations (in blue) are available in the appendix. The CNS, phrenic nerve(s), diaphragm and/or RAM may be involved. Insults can be gradual or sudden-onset, unilateral or bilateral and incomplete or complete. Loss of neuromuscular function is incomplete in paresis (weakness) and complete in paralysis. Acute diaphragm weakness may worsen clinical course in chronic conditions, culminating in death by acute respiratory failure. Diaphragm failure (frank arrest) is an under-recognized cause of serious morbidity and many sudden deaths, particularly those from cervical soft tissue injuries and blunt abdominal trauma (severe winding injuries).

- **Examples of chronic inspiratory muscle weakness conditions** included neurodegenerative and progressive myopathies. Skeletal muscles of the limbs, trunk and inspiratory muscles may become progressively weaker over time.

- In advanced stages, life-threatening respiratory muscle failure (frank diaphragm arrest apnea) can suddenly develop. This may occur from an added ventilatory workload on the diaphragm (and heart), even from a typically benign URI. Increased airway resistance and an increased respiratory rate (tachypnea) in response to infection, pleural effusion or congestive heart failure could tip the balance.

- **Acute inspiratory muscle weakness** can also cause sudden respiratory failure deaths. This included injuries to the spinal cord or bilateral phrenic nerves, both which can paralyze the diaphragm (i.e. ADP). Similarly, diaphragm injury (myopathy) from COVID-19 virus was confirmed at autopsy in adult ICU patients who had died by rapid respiratory failure [10]. Progressive muscle damage of diaphragm and RAM had occurred. Other examples included exposures to neurotoxins (already mentioned), venoms (snakes, spiders, jellyfish) and even extreme heat, such as vehicular heatstroke and malignant hyperthermia (the latter an adverse effect of certain anesthesia medications including succinylcholine).

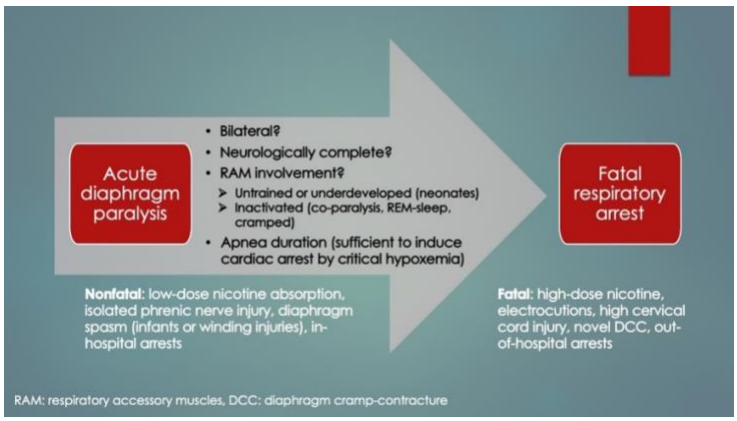
- From this knowledge, we determined that rapid onset respiratory muscle weakness from all causes was an underrecognized cause of serious morbidity (respiratory distress and brief apneas) as well as mortality in all ages (sudden deaths by ADP respiratory arrest).

  - One particularly heartbreaking case was a 13-year-old girl who tripped and fell in gym class while trying to jump a hurdle, striking the back/base of her head and neck on the crossbar (*Davis & Glass, 2001*) [11]. She died immediately. At autopsy was a large soft tissue neck contusion (collection of blood and swelling under the skin). There was no visible spinal cord injury explaining the sudden death, so the authors hypothesized she had died from a severe concussion (traumatic brain injury). However, given our fresh perspective, we considered that bilateral phrenic nerve compression, stunning (neuropraxia) or stretching (traction) at their roots in the neck by the contusion could have inactivated them, causing ADP respiratory arrest.

ADP can be immediately fatal when it is bilateral, neurologically complete (inactivates the diaphragm completely) and occurs in those with weak, paralyzed or cramped RAM (where they fail to independently take over the work of breathing).

  - DCC in very young/preterm infants satisfies these criteria because they have underdeveloped and untrained RAM.
  - RAM recruitment and training otherwise occur with maturation, and especially if: (a) diaphragm weakness starts gradually, (b) it is unilateral or (c) is partial (i.e. incomplete diaphragm paralysis, also known as paresis).
  - For the 13-year-old girl above, we speculated her RAM were paralyzed simultaneously with the diaphragm. That in addition to bilateral phrenic nerve injuries, the neck contusion also disrupted the nerves supplying her bilateral ICM (the intercostal nerves).

- Also, for ADP to be fatal, sufficient time needs to elapse for the hypoxemia to induce cardiac arrest and death (1-2 min and up to 10 min, respectively). So, *the ten-minute window offers an opportunity for resuscitation.*



- Supporting evidence: Experimental paralysis of the diaphragm (by severing the bilateral phrenic nerves) caused rapid death in newborn (neonatal) test animals, whereas older infants survived. *Hypothesis: Their more mature RAM were able to resume work of breathing independent of the diaphragm, whereas neonatal RAM did not.*
- **This demonstrates how, as compared to older infants, the very young (and premature) are highly vulnerable to respiratory failure deaths: because of weak, incompletely developed, untrained respiratory muscles**. It also supports our claim that RAM in young infants cannot independently ventilate the lungs when breathing against an inactivated diaphragm.

Diaphragm Fatigue, Hypertonicity and Excitation

- Unlike diaphragm weakness, diaphragm fatigue is reversed by rest.
- Because of the continuous nature of the respiratory cycle, the diaphragm is constantly cycling between contraction and relaxation. Whereas limb muscles which can rest when inactive, this is not possible with the diaphragm. Also, rest can only occur during the expiration (relaxation) phase, again reducing available time for muscle recovery to occur. This becomes even more problematic under increased respiratory rates, say during exercise or illness, when there is even less relaxation time. As a consequence, **diaphragm fatigue becomes a serious issue and manifests as reduced contractility, increased muscle tone (hypertonicity; from incomplete relaxation) and neuromuscular excitation**. In fact, hypertonicity might serve as a surrogate marker of fatigue (on diaphragm EMG).
- In contrast, relaxation times in skeletal muscles become *prolonged* under a number of conditions: (a) higher workloads (lusitropy), (b) hypoxemia, (c) hypercapnia, (d) acidosis and (e) bacterial endotoxins. This appears to be an adaptive response to maintain respiratory system homeostasis (balance), however, has its limits. When overcome in skeletal muscles or the heart, hypertonicity and pump failure ensue, respectively.
- Other outcomes of severe skeletal muscle fatigue in general include excitation-contraction uncoupling, loss of membrane integrity (muscle cell damage) and electrolyte imbalances [e.g. potassium (K^{+}), calcium (Ca^{+2}), magnesium (Mg^{+2}), phosphate ("Phos")].

- When blood supply of oxygen and other metabolic substrates (glucose and electrolytes) to the diaphragm become outpaced by demand, metabolic mismatch occurs. This is the basis of muscle fatigue. Also, accumulation of metabolic by-products occurs [such as acidic hydrogen ions (causing local acidosis) and phosphates]. Contractile dysfunction ensues, forcing the muscle to work harder.
- **Fatigued limb and trunk muscles become prone to neuromuscular excitation under increased workloads**. This is experienced by us all, especially when unfit, overheated or dehydrated (with acidosis). Excitation is triggered upon initial shortening (contraction) of the muscle.
- Examples of skeletal muscle neuromuscular excitation include transient twitches (fasciculations and spasms), myoclonus and sustained cramp-contractures.
- The diaphragm too is vulnerable to excitation; however, less is known about it. Unlike a limb cramp, the diaphragm is internally located, so cannot be aborted by stretching [*yet Patient 0's rescue breath technique somehow did*].
- **Young infants (under 4 months' age), compared to older, are especially vulnerable to diaphragm fatigue** because of numerous factors: a compliant ribcage (increased WOB), weaker, less developed respiratory muscles (strained under higher respiratory rates/demand), less fatigue-resistant diaphragm muscle fibers, higher metabolic and resting respiratory rates, and smaller lung airspaces (occlusion and added WOB from respiratory infections like RSV bronchiolitis).
- Numerous diaphragm fatiguing factors are thought to act (and interact) synergistically, raising the potential for diaphragm excitation. We used the term, *critical* diaphragm fatigue, to describe when the threshold for excitation is exceeded. And all that is needed to trigger is a workload surge, a sudden reduction in muscle contractility or relaxation becomes abruptly delayed.
- **Table 2** (below) lists the conditions in infants contributing to **respiratory fatigue and added WOB**. As opposed to muscle *weakness* factors seen in Table 1, these are generally reversible or temporary. **Many overlap with known SIDS risk factors.** This supported our (and others') hypothesis that critical diaphragm fatigue and workload surges predisposed some infants to ventilatory failure by DCC in SIDS.
- **Critical acidosis (and extreme hyperkalemia)** were reported at SIDS autopsies in 2006 but never corroborated. These commonly accompany bacterial infections and sepsis and have detrimental effects on skeletal muscles, perhaps lowering excitation threshold [12].
- Another reported fatiguing condition was **viral-induced diaphragm inflammation (myositis) and injury (myopathy)** [see *Diaphragm Injury at Autopsy* below]. This might cause contractile dysfunction (predisposing to excitation). Cases were reported in children with RSV, rhinovirus and Coxsackie virus, and in adults with COVID-19. RSV tends to have more severe symptoms than other respiratory viruses and is known to present with apneas and sudden unexpected deaths in young infants [13]. Other respiratory viruses were suspected by us, particularly influenza, because it similarly causes calf muscle myopathy in children, however, no pathology reports specific to the diaphragm were available to our knowledge. Gastrointestinal viruses might also infect the diaphragm, such as adenovirus, rotavirus and norovirus, however, diaphragm reports were unavailable.

- In **REM sleep**, to avoid physically acting out our dreams (which can cause injuries), the CNS has evolved to inactivate limb and trunk skeletal muscles by "tonic inhibition" (sleep atonia). A dreaming dog in REM sleep serves example, as exhibited by muffled barking and restricted running movements. Although the diaphragm is spared from atonia, RAM and upper airway "dilator muscles" are not (the latter traditionally held to cause OSA). In both cases, a sudden ventilatory workload is shifted to the diaphragm.

Diaphragm workload surges are known to arise from REM sleep and sudden-onset tachypnea. We added a position change to prone, diaphragm myositis/myopathy and diaphragm-stimulating seizures. Tachypnea occurs in respiratory and gastrointestinal infections, noxious stimuli like pain and loud noises as well as intense emotions like anger or anxiety. Severe hypoxemic/cyanotic episodes in infants were more common when household tension was high [14]. Infection, particularly respiratory, increased the frequency and severity of events probably because of added fatigue and workload triggering diaphragm excitation.

Avoid startling baby with loud noises, arguments or anything else that might increase household tension. These can trigger a breathing emergency.

In a supine-sleeping infant with critical diaphragm fatigue, diaphragm excitation can be triggered by REM sleep workload surges (i.e. inactivation of RAM and airway dilator skeletal muscles). In other words, **REM sleep could represent a SIDS catalyst.** This is consistent with the nocturnal, sudden and unpredictable nature of SIDS, as well as Patient 0's respiratory arrests.

- It is clear then in infants, a complex interplay of respiratory weakness and dynamic fatiguing factors superimposed on heightened vulnerability to fatigue contribute to potential diaphragm overload by a workload surge that catalyzes neuromuscular excitation as brief DS apneas and sustained contraction DCC respiratory arrests that could cause SIDS-like deaths.

Diaphragm Fatigue/Excitation Factors in Infants	Notes	Citation
Prematurity, Lower Birth Weights and Age Under 4 Months: Weaker, fatigue-prone diaphragms under high workloads. Putative excitation as DS presents with apneas-hypopneas, forced expirations, periodic breathing and hiccups, most with recurrent HE. Symptoms improve with respiratory muscle maturation.	Reduced contractility and added WOB: from underdeveloped muscles (fewer fatigue-resistant myofibers and lower cross-sectional area of all myofiber types), surfactant deficiency, cartilaginous ribcage, untrained RAM, inefficient diaphragm and RAM contractions. Compounded by malnutrition and hypoxemia of prematurity. The latter occurs in a positive feedback cycle (HE > reduced contractility > overload > excitation > more HE).	1-5
Young Infancy: Resting tachypnea and higher metabolic rate (both add WOB).	Narrower upper airway and bronchioli compared to older infants, excess pulmonary fluid, added anatomical dead space, RDS and BPD (in preterms).	6
Male Sex: Fatigue-prone, harder working respiratory muscles compared to females. Evident as increased *night sweats* (older male children and adults too). HE are more frequent and desaturations are worse.	Evidence for diaphragmatic basis of gender gap includes delayed respiratory muscle maturation, thinner diaphragms, higher airway resistances and increased night sweats and GERD in males (from putative DS). Also higher incidence of influenza myopathy and elevated CK levels. Higher mortality and co-morbidities in infant males, particularly preterms, occurs by repeated HE-ischemic injury, probably worsened by sepsis and acidosis.	7-12
Sleep: Added diaphragm WOB from airway obstructions, prone position and especially REM sleep (from CNS inhibition of RAM). Reduced arousal thresholds to HE/hypercapnia → no recruitment of RAM.	HE are more common in prone position and worse in REM sleep (more apneas-hypopneas and periodic breathing) and with reduced arousals. Fewer arousals observed in preterms and future SIDS victims.	1, 3, 12-16
Increased Lung and Airway Resistance (added WOB): RDS, BPD, pneumonia, bronchiolitis, bronchospasm, laryngospasm.	Treatable/preventable by RSV and pneumonia vaccines, antibiotics, bronchodilator medications. Evidence for DS included increased HE in BPD and apneas in RSV.	17-19
Nicotine: Exposure/absorption from household tobacco smoke in sleeping infants inducing diaphragm fatigue and putative excitation .	High potency neuromuscular blocker causing death in 5-30 min from overdose in young children. Scant amounts taken orally induced excitation (limb cramps and DS, including hiccups), followed by rapid respiratory arrest from diaphragm paralysis.	3, 20-23
Overheating (external factors) and Hyperthermia (internal): Reduced diaphragm contractility in both. Overheating is caused by fever, over-bundling and synthetic fabrics, and can be prevented. Malignant hyperthermia *overlaps with diaphragm-cramp respiratory arrest* , both involving skeletal muscle rigidity, spasms and contractures.	Apnea frequency in young infants increased significantly with increasing temperatures in REM sleep but not in non-REM sleep. Acute hypercapnic respiratory failure occurs in malignant hyperthermia (diaphragm failure).	3, 24-28
Viral and Bacterial Infections (including sepsis): Diaphragm damage from viral myositis (inflammation) and myopathy. Both overlap with painful limbs in pediatric influenza (calf muscle myopathy). Diaphragm myopathy was also reported in sepsis, heat stress, hypoxia and excessive inspiratory workloads. Reflected by elevated CK levels and apneas/respiratory arrests in RSV infections.	Acute infections in ICU patients reduced diaphragm strength by ~80% within 24 hours. Fatigue and sudden peripheral respiratory failure were demonstrated experimentally. Worsened by hypoxemia and acidosis. Pathogens: bacterial toxins and viruses such as RSV, adenovirus and coronavirus (possibly influenza and rotavirus too). Elevated CK levels in healthy neonates were associated with acidosis, lower 1-min APGAR scores and asphyxial deaths (presumed HE-induced diaphragm injury).	29-37
Hypovolemia (dehydration) and Hypotension: Dehydration occurs by sweating and GI fluid losses, primarily. Hypotension occurs in shock, which has numerous causes (septic, hypovolemic, cardiogenic, etc). Diaphragm fatigue and delayed relaxation occurred from hypoperfusion in experimental septic, hypovolemic and cardiogenic shock.	Excessive sweating contributes to cramps of limb muscles (*and diaphragm)* , especially when acidosis, electrolyte disorders and hypoxemia are present. Also, diaphragm hypoperfusion in shock → reduced oxygen and metabolite delivery → reduced diaphragm contractility → respiratory muscle fatigue and failure (latter by sustained contraction from "electromechanical dissociation", *Hussain* [39]).	38-40
Anemia (low hemoglobin): Diaphragm fatigue occurs by a reduced oxygen-carrying capacity of blood. Supported by a higher incidence of apneas and ALTEs in young children.	ALTE were worse 1-week post-URTI (*perhaps by slowly developing viral myopathy of diaphragm*). Fewer apneas occurred after blood transfusion.	41,42
Metabolic Acidosis (low blood pH, typically from lactic acidosis): Reduces diaphragm contractility, delays relaxation and increases muscle excitability. Acute respiratory muscle failure occurs in DKA and is *perhaps not centrally induced from cerebral edema (in fact, cerebral edema is thought to be a complication of DS, from IVC and aortic clamping).*	Causes: dehydration/hypovolemia, bicarbonate-loss diarrhea, URTI, sepsis, tissue hypoxia seizure activity, parenteral nutrition. In Kussmaul's breathing (compensatory deep breaths in acidosis to "blow off" CO_2), the increased WOB and high ventilatory drive *can exacerbate diaphragm fatigue, leading to peripheral respiratory failure from DCC.*	34,43-45
Respiratory Acidosis (hypercapnia = high pCO_2): From hypoventilation or rebreathing exhaled gases. Induces diaphragm hypertonicity, reduced contractility and prolonged expiration phase (relaxation).	Preventable by ventilating bedroom and avoiding prone sleep position and co-sleeping as well as gas pooling from soft bed linens, bumpers and bed toys. Do not let infant sleep/rest on a person's chest or sofa (rebreathing, overheating & higher WOB).	46-48
Hypoxemia (low pO_2 levels): Reduces diaphragm contractility and prolongs relaxation. Positive feedback cycle through the diaphragm. Supported by reports of increased apneas at high altitudes.	Occurs by reduced alveolar gas exchange [RDS, surfactant deficiency, pulmonary infiltrates and atelectasis (pneumonia and RSV)] as well as from BPD, bronchospasm, vascular shunts and fetal hemoglobin (local hypoxemia in diaphragm).	21,46,49
Electrolyte Disorders: Ca, Mg, Phos, Na, K. Worse with acidosis and hypoxemia. Respiratory paralysis-failure a common endpoint for all. Sustained muscle contractions (contracture), spasms and impaired relaxation (e.g. hypocalcemic tetany).	From fluid losses (sweating, vomiting, diarrhea) and malnutrition. Various effects on muscle excitation-contraction coupling. Replacement of Mg reduced weakness and recurrent apneas. Phosphate improved diaphragm weakness.	50-52
Endocrine Disorders: Respiratory weakness from hormone excesses/deficiencies with associated electrolyte imbalances and metabolic dysfunction.	E.g. hypo/hyperthyroidism, hyperglycemia with acidosis (DKA), excess corticosteroids or catecholamines (epinephrine, norepinephrine). Epinephrine induced diaphragm contractures in vitro.	53-55
Neurologic and Myopathic Diseases: Respiratory failure is the most common cause of hospitalization and death, commonly triggered by URTI. E.g. multiple sclerosis, poliomyelitis, Guillain-Barré, muscular dystrophy, malnutrition, corticosteroids.	Nocturnal hypoventilation and HE are more common during sleep, particularly in REM. Bilateral diaphragm weakness has significantly worse prognosis than unilateral, where survival likely depends on *arousability* and *RAM compensation* to REM sleep diaphragm failure.	56-58
Prolonged illness (bedrest) and MV in critical care patients lead to respiratory muscle weakness. 60-80% of MV patients have clinically significant diaphragm fatigue.	Occurs from disuse atrophy, myopathy, systemic inflammation and reduced diaphragm perfusion. Also, WOB is increased from lung injury, infection/sepsis and fluid overload. All can lead to sustained respiratory failure in MV patients.	29,34,59
Seizures (focal and generalized): Phrenic nerve-diaphragm hyperstimulation, apneas, hypopneas, hyperpneas and cyanotic HE, all worse in REM sleep. Sleep-disordered breathing is more common in epilepsy.	Deaths are known to occur by terminal apnea either during or after seizure. Diaphragm arrest is *proposed to occur from work overload* by seizure itself or postictal REM sleep, prone positioning, compensatory tachypnea, critical lactic acidosis and/or critical hypoxemia.	60-62
Acutely Increased WOB: From psychological distress, noxious triggers (pain, airway suctioning, loud noises) or bottle feeding. All worsen fatigue.	Are associated with apneas, cyanotic HE, ALTE and seizure-like activity. Proposed to occur by *diaphragm overload and excitation.*	63-65

ALTE: apparent life-threatening event, BPD: bronchopulmonary dysplasia, CK: creatine kinase, DKA: diabetic ketoacidosis, DCC: diaphragm cramp-contracture, DS: diaphragm spasm, HE: hypoxemic episodes, MV: mechanical ventilation, OSA: obstructive sleep apnea, PDA: patent ductus arteriosus, RAM: respiratory accessory muscles, RDS: respiratory distress syndrome (neonates), RSV: respiratory syncytial virus, URTI: upper respiratory tract infection, WOB: work of breathing, *Italics* : putative (unproven).

Table 2: Causes of inspiratory muscle fatigue in infants. Citations (red) are available in the appendix. Fatiguing factors are thought to act synergistically in an individual, raising the potential for diaphragm excitation.

Hypotheses (summary):
In young infants, respiratory muscle weakness from incomplete development + cumulative effect of fatiguing factors + limited ability of diaphragm to rest → increased risk for critical fatigue. This is when the threshold for excitation is exceeded, and all that is needed to trigger it is an added workload.

1. In all ages, critical diaphragm fatigue + ventilatory workload surge → excitation → diaphragm spasms (DS, including hiccups), myoclonus (DM), flutter (DF) or cramp (DCC). It is unknown why one form occurs over another; however, DS appears to be most common. Varying arousal thresholds from sleep hypercapnia in infants may play a role (i.e. hypercontraction stops with waking up, followed by reactivation of RAM, deeper breaths and increasing oxygen levels).
2. Diaphragm fatigue → incomplete relaxation after each contraction → increased muscle tone (hypertonicity) → diaphragm excitation
3. Incomplete relaxation → lung air trapping (breath stacking) → hyperinflation → diaphragm thinning → mechanical disadvantage → diaphragm pump insufficiency → lung alveolar hypoventilation → hypoxemia and hypercapnia → more fatigue (positive feedback cycle).
4. Reduced diaphragm blood supply (perfusion) in tachypnea → diaphragm fatigue → hypoxemia and hypercapnia → worsening tachypnea + reduced perfusion? (positive feedback cycle).

Respiratory Instability in Preterm Infants

- Given SIDS affects young infants most commonly (age peak at 2-4 months old), we explored the medical literature on early infancy. Unsurprisingly, respiratory pathology was the primary issue and worsened with younger age, lower birthweight or increased prematurity. Many preterm babies require extended periods of MV in the neonatal ICU as a result. Also, males are affected more often and more severely than females (see *Male Preponderance* below). Fortunately, most appear to outgrow it by the fourth week of life. This too supported the notion that **incomplete respiratory development is associated with SIDS**. Our hypothesis diverged from mainstream ideas concerning CNS immaturity and central apneas. Incomplete respiratory muscle development with consequent vulnerability to fatigue, overload and sudden failure represented **peripheral apneas** (not central).
- **Respiratory instability** (**RI**) is a general term that can be applied to describe the variety of breathing abnormalities observed in infants in the ICU and associated with **hypoxemic episodes** (**HE**) [14, 19, 23]. Notably, all are transient (brief), and some were associated with silent squirming: forced high-volume expirations (or hyperpneas), apneas (most are under 10 s but become worrisome at 20 s), hypopneas (shallow breaths from airway obstruction), pallor/cyanosis, bradypneas (reduced respiratory rates), bradycardias (typically following apneas-hypopneas), periodic breathing (alternating cycles of tachypneas and brief apneas) and increased arousals (fragmented sleep). Hiccups, which are more common in younger infants, could also be included here, especially given spells occur often in this age group, many with subsequent apneas and hypopneas [15]).
- Although many HE occur without overt signs of infant distress (because of short duration), others can present with a wide variety of gastrointestinal and neurologic symptoms (in addition to those above): gastroesophageal reflux and feeding difficulties, loss of muscle tone (hypotonia or

floppiness), back arching and other unusual posturing, seizures and/or loss of consciousness. It is important to realize that unwitnessed crib deaths could also be a presentation (i.e. SIDS).

Frequent hiccups in an infant could indicate diaphragm fatigue. See a doctor immediately if there is fever, respiratory infection, diarrhea or any breathing problems (i.e. rapid rate, pallor, cyanosis, breathing pauses, retractions).

- Although the cause of RI has never been elucidated (only speculated to be from CNS immaturity, intermittent airway obstructions of unknown origin or abdominal muscle contractions), **the pathologic agent nonetheless is intermittent hypoxemia** (HE). Although brief HE appear tolerated, they can be dangerous, both immediately (when prolonged), or collectively, accumulating over the course of several weeks to months if not longer in some infants. In other words, there are serious short- and long-term complications.
- Literature review indicated HE may strike when a baby is awake or asleep and were **worse during REM sleep** (more frequent and prolonged). They were also more common when bottle feeding [5, 6, 14] and if respiratory infection was present [14].
- Defined as oxygen saturations under 88% for over 10 s (normal is above 96%), HE can vary from tens of seconds to two minutes and may occur hundreds of times daily (a cumulative danger). Saturations can even dip below 70% in some cases and for several minutes at that; a respiratory emergency given hypoxic brain injury begins after 3 minutes.
- Short term complications (morbidities) of recurrent HE in early infancy include cerebral hypoxemia (causing anoxic seizures, hypotonia, brain injury and/or coma), brain (intraventricular) hemorrhages, bronchopulmonary dysplasia (BPD), acute pulmonary hypertension, poor feeding/weight gain and increased risk of necrotizing enterocolitis (inflamed intestines) and serious infections like bacterial sepsis. **Sudden respiratory arrests are also a concern**, especially in those with co-morbid disease (i.e. cardiac, respiratory, neurologic, myopathic or metabolic conditions).
- Long term morbidities of HE include visual and hearing deficits, growth and neuro-developmental delays, cerebral palsy (in birth asphyxia [16]), as well as chronic pulmonary hypertension, structural heart diseases (cardiomyopathies) and also sudden respiratory arrests in the first 18 months of life from sudden unexplained deaths (consistent with SIDS and SUDC) [14, 17]. **Preliminary evidence in neonatal rats exposed to 90 min of postnatal hypoxemia suggested a connection to attention-deficit hyperactivity disorder (ADHD)** [18].

Critical diaphragm fatigue with hyperexcitability is responsible for RI in infants and the HE that follow them. REM sleep inhibition of accessory muscles is the primary trigger during sleep. Increased diaphragm fatigue and workload by respiratory infections could explain why HE were more frequent when infection was present.

- This hypothesis was best supported by studies employing gastric pressure sensors and abdominal surface EMG in infants (using sticky leads like a heart ECG but measuring underlying skeletal muscle activity instead). As can be seen in **Fig. 1** below, preceding each HE (blue ellipse) was a burst of muscle contractions associated with forced expirations and transient apneas (red boxes).

Instead of the abdominal muscles being solely responsible, we proposed it was simultaneous diaphragmatic ± abdominal contractions (like RF but in the form of short twitches and spasms).

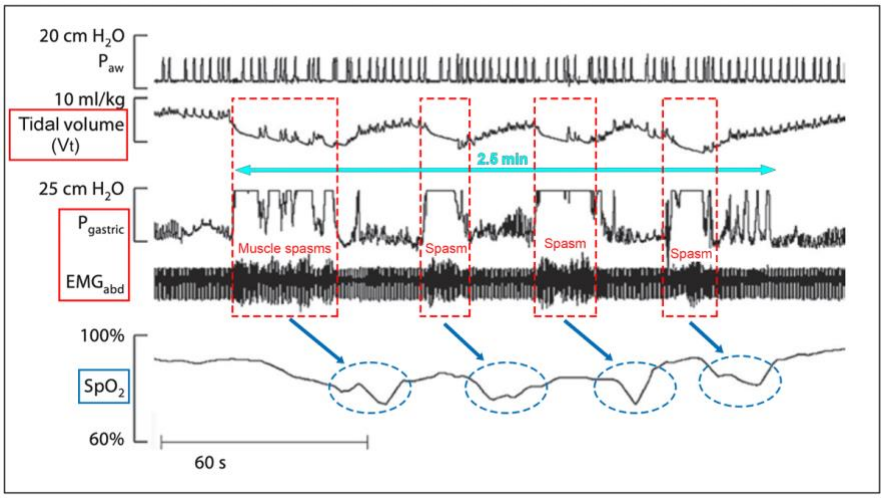
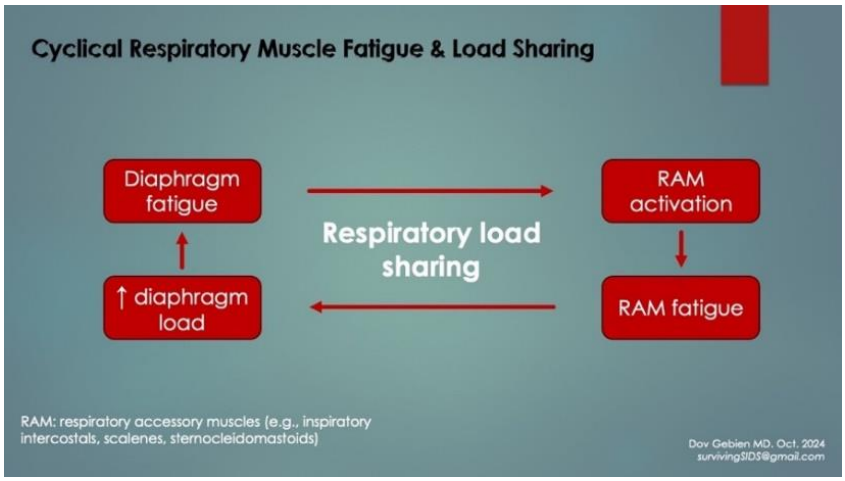


Image reproduced with permission. Source: Esquer C, et al. Copyright © 2007 Karger Publishers, Basel, Switzerland [19].

Fig. 1: Mechanically ventilated preterm infant with intermittent hypoxemia. Cyclical apneas and hypopneas are seen in the tidal volume (Vt) waveform, demonstrating periodic breathing. "EMG_{abd}" was thought to measure abdominal muscle electrical activity. However, if that were true, then this mechanically ventilated preterm infant repeatedly tensed theirs (and briefly held their breath intermittently) for 2.5 min (cyan arrow), to the point of dropping oxygen saturations under 75% four times (blue arrows and ellipses). By contrast, healthy adult volunteers could not reproduce that [14]. Instead, spontaneous involuntary diaphragm ± abdominal spasms could have been responsible. Given the diaphragm is the primary ventilatory muscle, it is much more likely to affect respirations than would the abdominal muscles (which are accessory). Delayed oxygen desaturations are a normal finding with the technology used.

Periodic breathing too could be explained by repetitive cycles of diaphragm fatigue (with ensuing overload and DS) alternating with RAM fatigue (overload and spasm too), whereby workload is diverted from one group to the other via respiratory load sharing. In the image above, each brief apnea (Vt flatline) is associated with a DS spike and followed immediately by rapid breaths. The latter could reflect physiological compensation to the hypoxemia (and hypercapnia).



Obstructive Sleep Apnea (OSA) in Children and Adults

- OSA in older children (and adults) is a highly prevalent, underdiagnosed condition. It is often silent, so is missed by parents. Older individuals may not even know they have it, which presents a problem because of serious medical complications.

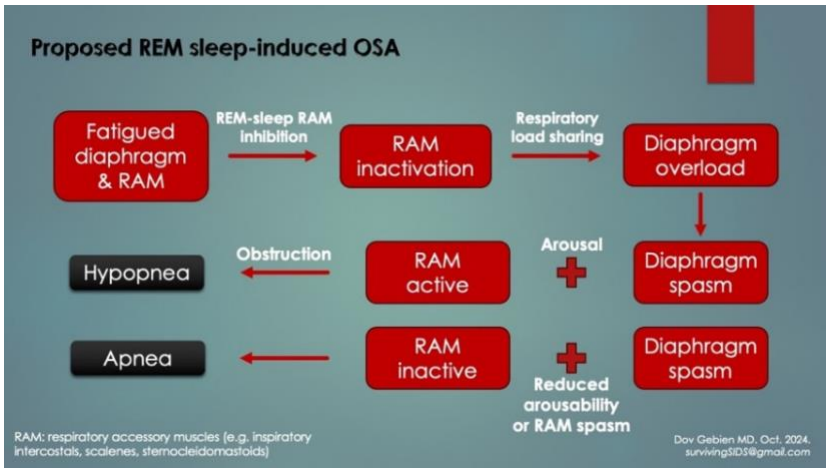
If you suspect breathing pauses or obstructed breaths in your sleeping child, have them seen by a pediatric sleep specialist for testing. A pediatric CPAP mask might be indicated.

- **Like RI in infants, OSA also involves repeated apneas and hypopneas**. These too are more common during REM sleep and associated with night sweats, worse in males (overlapping SIDS risk factors). Night sweats might reflect higher heat output of harder working respiratory muscles. Frequent arousals also occur in OSA, waking up gasping or choking for several seconds.
- Like RI, OSA too carries significant short and long-term morbidities as well as higher overall mortality. In adults these include systemic and pulmonary blood pressure surges (leading to a diagnosis of chronic hypertension), cardiomyopathies (abnormal heart chamber dilatations or wall thickenings) with resultant congestive heart failure (pump inefficiency causing pulmonary edema), heart valve disorders, coronary artery disease (angina and heart attacks), cardiac arrhythmias, stroke (acutely reduced cerebral blood flow), venous thromboembolism (blood clots, typically in the legs) and an increased risk for sudden cardiac deaths (SCD). In one study, SCD occurred most often during sleep hours (12-6 am) in those with OSA compared to SCD in control subjects, where the risk of SCD correlated to the severity of OSA (more apnea-hypopnea events).

OSA has historically been explained by reversible collapse of the upper airway dilating muscles during sleep. Instead, we suggest this is not the primary cause, but rather how it contributes to DS apneas-hypopneas because of its added airway resistance (higher diaphragmatic workload).

Like RI in infants, we propose OSA in older children and adults is caused by DS. That OSA and RI are *one of the same*.

The novel airway obstruction of DS in OSA develops when RAM contractions to breathe are resisted by the hypercontracted, incapacitated diaphragm. This produces the low volume hypopneas. Again, it can be triggered by REM sleep and other workload surges.



- Evidence linking diaphragm pathology to RI/OSA was provided by four important studies:

    1. In 13 preterm infants with apneas, expiratory time and total pulmonary resistances increased in the breaths immediately preceding apneas that could not be fully accounted for by supraglottic resistance (i.e. constrictions of the upper airway dilator muscles or other soft tissues) [20]. Along with Southall's findings of continued HE in infants despite tracheostomies or endotracheal tubes in place, upper airway obstructions were not the cause of the increased-resistance apneas. Something else had caused it (laryngospasm and bronchospasm were mentioned but not proven).

    2. In 21 adults with OSA, activation of the respiratory muscles (airway dilators, ICM and diaphragm) was compared with those of healthy control subjects using EMG. All muscles were more active in those with OSA, both awake and asleep, reflecting a chronically increased diaphragm workload [21].

    3. In another adult OSA study by the same group, one polysomnogram image showed a 30 s apnea (shaded red box in **Fig. 2** below) associated with sudden cessation of chest and abdomen ventilatory movements consistent with a central apnea (i.e. lack of neurally stimulated breathing) [22]. However, because diaphragm electrical activity did not cease (active in 'EMG1-5"), the diagnosis was changed to obstructive apnea. The problem with that, however, was obstructive apneas normally involve continued respiratory efforts, which were not present, so something else had to be responsible. The clue was in the D-EMG waveforms, which were reduced in intensity during the apnea. We believed peripheral malfunction (of both diaphragm and RAM) had taken place, where electromechanical failure had occurred (i.e. despite phrenic nerve stimulation, the inspiratory muscles had failed, causing the HE).

    4. In an EMG study of an infant with a HE cyanotic squirming episode [23] (**Fig. 3**), although diaphragm activity was not measured (like Fig. 1 above), surface abdominal EMG was used. It demonstrated increased muscle activity for 50 s that disrupted normal (tidal) breathing. A sustained elevation of esophageal pressure also occurred and was thought to be due to abdominal muscle contractions (perhaps voluntary). We felt spontaneous diaphragm contractions could have contributed to this, given the electrical activity could easily cross-contaminate the surface EMG. This made more sense given the numerous ventilatory issues observed and especially because this was a very young, weak and likely malnourished preterm infant, again highly unlikely to contract their abdominal muscles for such an extended period and to disrupt breathing to such an extent as to cause cyanosis. Interestingly, the episode was silent too (no crying), consistent with diaphragm arrest [from DS].

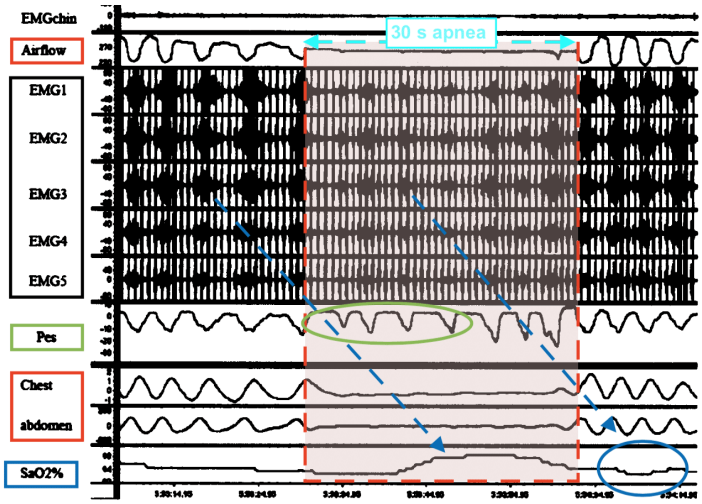


Fig. 2: Brief sleep apnea in an adult with abnormal diaphragm EMG. Airflow and respiratory movements (*chest* and *abdomen*) cease at the same time as a reduction in EMG waveforms. Somehow, the diaphragm and inspiratory RAM had failed to produce sufficient force to create airflow. We proposed the diaphragm had been inactivated during the first part of the apnea (cause unknown), resulting in mechanical failure of respirations. Continued P*es* (esophageal pressure) hypopnea waves (green ellipse) were thought to reflect the work of independent RAM contractions. These were ineffective at first; unable to produce airflow. But as the diaphragm "came back online" during the apnea (activated for 3 waves after the ellipse in P*es*, with increasing electrical intensity of neural stimulation), with continued RAM efforts, subsequent mechanical strength increased sequentially until the apnea was finally overcome. This was not a central apnea because D-EMG activity did not cease at any point (it is a surrogate of neural breathing).

All novel information provided here in this summary paper (and the original), claiming diaphragm failure in RI and SIDS, boils down to Figures 2 and 3.

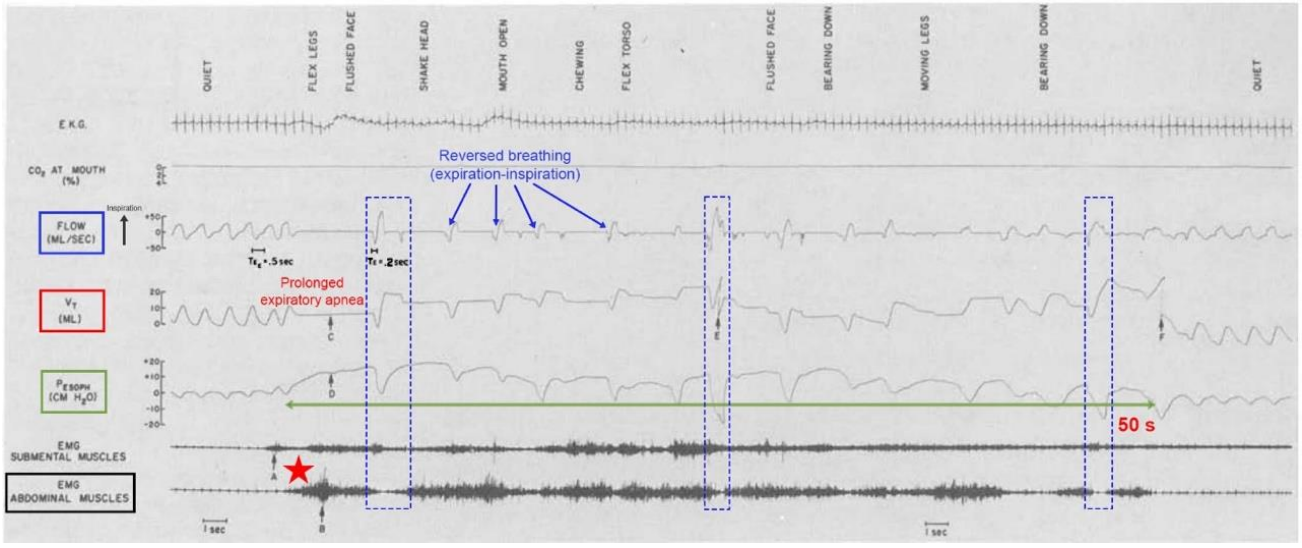


Fig. 3: Sleep polysomnograph with *surface* EMG in a preterm infant with a silent squirming cyanotic episode. Although oxygen saturations were not measured, ventilatory abnormalities were significant. The event begins at the red star, when EMG increases. A 4 s apnea occurs while in expiration ("C"). Esophageal pressure rises (P_{ES}, starting at "D") and remains elevated for 50 s (above green line), when several breathing abnormalities occur [seen in V_T (tidal volume) and flow]. This included a reduced respiratory rate and several hypopneas where respirations appear to occur *in reverse*. The V-shaped negative deflections (drops) in P_{ES} over this time were likely the result of inspiratory muscle contractions

stimulated by neural breathing. When EMG abates, hyperpneic breaths are taken (blue boxes), perhaps as compensation to hypoxemia. Interestingly, the baby did not cry. We proposed that "EMG abdominal muscles" was from spontaneous (and involuntary) contractions of the diaphragm and abdominal muscles. This would better explain the above abnormalities and rids any notion of a voluntary component to the abdominal muscle contractions.

Novel Mechanisms of Sleep Apnea

- Given this new mechanism of sleep apneas (peripheral malfunction of inspiratory muscles), we went on to suggest that classic sleep studies (employing airflow and chest impedance, CI, measurements) may be interpreted differently:
    - Central apneas: Instead of failure of neural breathing, it is simultaneous failure of RAM and diaphragm by REM sleep and diaphragm spasm, respectively.
    - Obstructive apneas: Instead of the diaphragm breathing against upper airway obstruction, it is RAM against the diaphragm briefly inactivated by DS.
    - Mixed apneas: Instead of combined central and obstructive apneas, these occur when one of the inspiratory muscle groups "comes online" over the course of an apnea. For example, RAM activation by arousal during a DS. Or DS offset with functioning RAM.
- Returning to the Patient 0's bearhug apnea, he could not inspire despite trying. Had respiratory flow and CI monitoring been used, it would have appeared as a central apnea because of lack of chest expansion. Yet, there was complete airway obstruction, and it was probably caused by co-cramping of diaphragm and intercostal muscles.

Diaphragm Failure in Sudden Unexpected Deaths

Whereas *transient* DS induces brief apneas with hypoxemic episodes (which are survivable), *persistent contractions* (as DCC) cause sustained apneas (respiratory arrests) leading to life-threatening critical hypoxemia. Cardiac arrest would occur in only 1-3 minutes. Moreover, triggered by REM sleep or prone positioning with other factors, fatigue-induced DCC would cascade in a nocturnal, silent and rapid respiratory arrest death consistent with SIDS.

Sleep DCC also occurs in older children and adults, leading to nocturnal silent deaths consistent with SUDC and SCD, respectively. However, are much rarer than SIDS because of more mature respiratory muscles (i.e. threshold for critical diaphragm fatigue is higher).

- Theoretically, for apnea/respiratory arrest to occur, there must be either: (1) a lack of neural stimulation (central apnea), (2) a complete airway obstruction (obstructive apnea) or (3) simultaneous failure of *both* diaphragm and RAM (peripheral apnea).
- Using classical CI technology (sticky leads on chest & abdomen) during a sleep study, the following have been interpreted historically (inferred, but not definitively proven):
    - "Central" apneas = no airflow, no respiratory movements of chest/abdomen.
    - Obstructive apneas = no airflow but with respiratory movements of chest/abdomen.

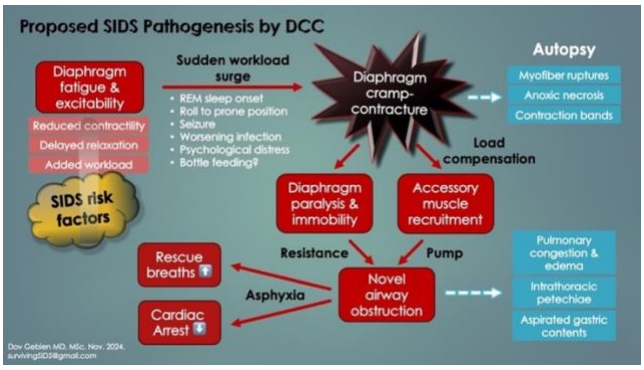
- Hypopneas (obstructed breaths) = reduced airflow, reduced movements of chest/abdomen.

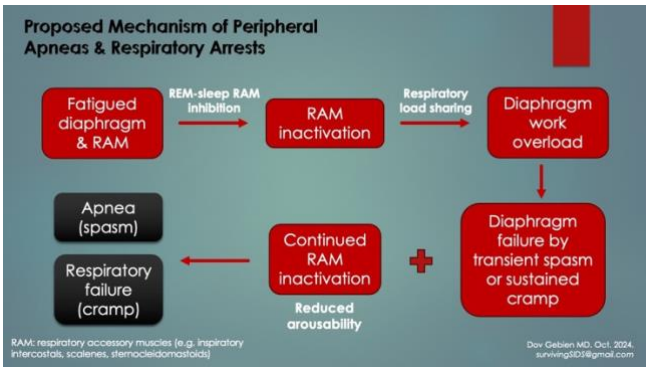
1. The diagnosis of a **central apnea** assumes the lack of airflow and movements are caused by no neural input to the diaphragm. It was inferred, not actually measured (because that would require surgical implantation of an electrode in the neck to measure phrenic nerve activity). Unfortunately, this line of reasoning has perpetuated throughout mainstream research for many years. Peripheral failure (of diaphragm and RAM) was not taken into consideration. However, when *Luo et al.* compared CI to diaphragm EMG, many central apneas were found to be peripheral [22]. Thus, true central apneas may not be as common as thought.
2. In addition, fatal spontaneous **airway obstructions** during sleep too have been called into question. The most commonly cited causes include laryngospasm (vocal cord airway closures) and atonic dilator muscles. In our opinion, both are insufficient as to cause agonal breathing, critical hypoxemia, cardiac arrest and death because they are either transitory or incomplete, respectively, or both. Also, Southall demonstrated in nine children under 22 months' age that severe HE still occurred despite endotracheal and tracheostomy tubes in place (keeping the airway free of obstruction). Together, this casted serious doubt about spontaneous airway obstructions causing respiratory arrest deaths [14], leaving the third option.
3. **Peripheral apneas/respiratory failure** presents a lesser-known mechanism of apneas; yet a non-spontaneous version has already been discussed (ADP in nicotine overdose, envenomations and succinylcholine). *Both diaphragm and RAM must fail simultaneously for this form of apnea to occur,* and appears to result by a variety of mechanisms:

    - In Patient 0 with complete respiratory arrest ("like a total airway obstruction"), we proposed there was simultaneous failure: (a) DCC and (b) cramping of ICM (co-cramping).
    - In sleeping infants with DS triggered by REM sleep inactivation of RAM, while this could cause a short apnea, sustained respiratory arrest would require the infant does not wake up to reactivate RAM. Impaired arousal has been considered a SIDS risk factor, so could explain this.
    - While the first two could cause respiratory arrests, they would not explain SIDS autopsy findings (i.e. evidence of obstruction). Something needed to provide inspiratory force (to generate the negative intrathoracic pressures) and also required breathing against some form of reversible airway resistance.
    - This could be explained by a combination of DCC with ineffective RAM contractions, due to their inherently weak state during young infancy (underdeveloped and untrained). Like the inspiratory mechanical failure shown in Fig. 2 above, RAM are hereby proposed to be semi-functional. Their action would generate inspiratory efforts and generate negative intrathoracic pressures yet fail to expand the lungs with air (ineffective gasping).

Like the hypercontracted, incapacitated diaphragm of DS mentioned above (causing brief apneas in OSA), **DCC itself is the mysterious airway obstruction in SIDS.** It would resist agonal RAM pumping actions, thus explaining autopsy findings. It would also disappear with postmortem relaxation, explaining why it has evaded detection all this time.

- The following two images provide a summary of our proposed SIDS pathogenesis based on the novel diaphragm pathology presented here.





Male Preponderance in Respiratory Instability and SIDS

- The male sex is a well-known SIDS risk factor, as 60% of victims are male (ratio of 1.5:1). This is an extension to the "male disadvantage" seen in respiratory morbidity and mortality in early life. Compared to preterm girls, preterm boys have more frequent and more severe HE along with its host of short- and long-term complications, including death from respiratory causes [17, 24]. Interestingly, there is also a male preponderance to cerebral palsy, ADD/ ADHD and autism [25], suggesting a common mechanism (which we think is recurrent HE from repeated DS in early infancy).

Compared to female infants, male diaphragms are more susceptible to fatigue and work overload, culminating in recurrent HE from pathological excitation and causing the RI and SIDS gender gaps as well as contributing to the likelihood of cerebral palsy, ADD/ADHD and autism.

- The overall supporting evidence for fatigue-prone diaphragms in males was compelling. Compared to females, males had thinner diaphragms on ultrasound (weaker and forced to work harder*), elevated total airway resistances (causing higher ventilatory workloads), reduced respiratory exercise endurances as well as less efficient diaphragm contractions and ICM recruitment. Also, male mice exposed to in-utero (birth) asphyxia had lower survival rates at one hour after birth compared to females (52% versus 69%, respectively) [26]. Their diaphragms had significantly worse structural and functional deficits, suggesting that hypoxemia-induced, gender-skewed diaphragm failure had caused the deaths. (*In that ultrasound study, the authors suggested the reduced diaphragm thickness translated to diaphragm weakness [27].)
- Unsurprisingly, adult males too have a higher incidence of OSA than females. Night sweats, also more common in men, could reflect the added work of breathing by a fatigue-prone diaphragm, especially in REM.
- Another surprise was a male preponderance of leg (calf) muscle inflammation (myositis) and damage (myopathy) in children and adults with influenza [28]. Perhaps the diaphragm too could become involved in these viral infections (viral myositis/myopathy)?

Viral-induced diaphragm contractile dysfunction (myopathic weakness, worse in infant males), combined with added resistance from upper airway and pulmonary congestion, could increase diaphragm workload, fatigue and potential for spontaneous DCC leading to SIDS. This would also explain the male SIDS predominance.

Diaphragm Injury and Congested Organs at SIDS Autopsy

- The strongest support for DCC in SIDS came from a systematic diaphragm autopsy study by *Kariks* (1989) [29]. Although macroscopic (gross) abnormalities were not seen, microscopy with special staining (histology) revealed **(1) myofiber ruptures and (2) diaphragm contraction band necrosis (CBN**) in 198 of 242 SIDS cases (82%), along with **fibrotic scars**. The CBN had occurred rapidly and terminally under severe hypoxia, close in time to the cardiac arrest. Despite a few other histological reports confirming these myopathic changes in SIDS, the line of research went inexplicably silent.

1. **Diaphragmatic CBN**: has also been reported in deaths from birth asphyxia (the most common category) as well as those from perinatal and infantile infections (second most common), including respiratory, gastrointestinal, bacterial sepsis and meningitis. Other deaths included motor vehicle accidents, anesthetics, drownings, asthma and carbon monoxide exposures (house fires and burns). Proposed causes of CBN included hypoxia-ischemia, viral myositis and metabolic mismatch (fatigue) with excess catecholamines [epinephrine (adrenaline) and other adrenal hormones].

The CBN-associated deaths from a variety of causes in children suggest a common mechanism. DCC could represent the terminal cause of death in all.

2. **Diaphragm myofiber ruptures**: Dr. Michael Eisenhut MD published an important report in 2011 (*who later became a co-author of the original DCC paper*). Tragically, a 5-month-old previously healthy girl who was admitted for viral respiratory infection (rhinovirus) and poor feeding (adenovirus) had died in hospital by a sudden unexpected respiratory arrest. Autopsy diaphragm histology revealed myofiber destruction, necrosis and regeneration as well as inflammation [30].

    - Similar abnormalities were also reported in sudden deaths in children and adults with viral respiratory infections from RSV, influenza and COVID-19 [10, 31]. All demonstrated that viral-associated respiratory arrests can occur suddenly, rapidly and unexpectedly in all ages, consistent with DCC myopathy.

    - In addition to viral myopathy, a clue to the origin comes from experimental loading of rabbit inspiratory muscles well above their fatigue thresholds [32]. In other words, breathing against a near-total airway obstruction (resistive breathing). Myofiber disruptions and significantly inflamed necrotic tissues were demonstrated in all test animals. Moreover, they occurred in a load-dependent manner whereby higher ventilatory workloads correlated to larger areas of damage (myopathy). There was no mention of D-CBN, however, none of the

rabbits had died during testing (presumably no DCC). Myofiber disruptions (but not necrosis or inflammation) were also seen in 29 of 29 human test subjects exposed to less severe inspiratory loading [33].

The airway obstruction of DS/DCC is the source of the diaphragm myofiber disruptions. With continued obstructed breathing under severe hypoxemia, necrosis develops (as CBN).

- **Organ weights in SIDS are significantly higher than normal**, including the brain, lungs, thymus, liver and spleen [34, 35]. Negative intrathoracic pressures (nITP) generated by breathing against obstruction partly explains the heavy, wet lungs because of blood pooling (shunting) into the pulmonary circulation (see *Pulmonary System* below).
- To explain this from a diaphragmatic perspective, we considered its 3-dimensional anatomy. Specifically, that the inferior vena cava (IVC) and aorta pass through its left-to-right axis in the perpendicular plane (up and down). They can be seen in cross section in **Fig. 4** below as they course through their diaphragmatic apertures (hiatuses or foraminae), passing from abdomen to chest and vice versa, respectively. The IVC — a major vein carrying deoxygenated blood away from the abdominal organs and lower extremities to the heart — and the aorta (artery transporting oxygenated blood away from the heart and lungs to all organs and extremities), are the two largest blood vessels in the body.

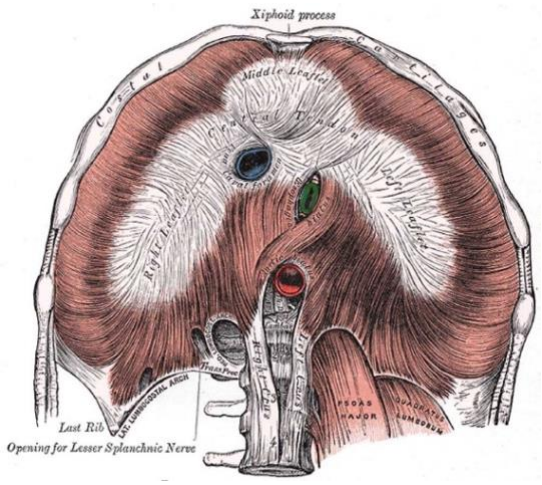


Fig. 4: Two-dimensional anatomy of the abdominal diaphragm (from below). The diaphragm is composed of strong tendons (white) and muscles (red brown), which tightly wrap around three important organs: the IVC, aorta and esophagus. Increased diaphragm muscle tone and pathological contractions (excitation) could effectively squeeze or completely clamp these structures at their hiatuses, potentially causing serious up- and downstream hemodynamic (and gastrointestinal) consequences. Courtesy of Henry Vandyke Carter. Public domain, Wikimedia Commons, 2008

- In diaphragm excitation, **the squeezing force of DS/DCC could partially clamp (occlude) these great vessels,** leading to reduced blood flow above and below the diaphragm but to different degrees, depending on location of the organ or extremity in question and position relative to the heart. Also, cardiac output, blood pressure and venous drainage would simultaneously be affected, all leading to reduced organ perfusion and injury.
- **Aortic clamping** at the diaphragm could induce an immediate hypertensive spike in organs and extremities above the diaphragm. Those below would likely face hypotension. The effects of **IVC clamping** on blood pressure would take longer to appear as venous congestion develops more gradually. Over time, less and less blood returns to the heart, worsened by nITP-pulmonary shunting. Ultimately, the combination of persistent IVC and aortic clamping and nITP in diaphragm cramp would eventually induce severe hypotension (shock).

- The **pulmonary system** presents a unique hemodynamic situation in DS/DCC because of its blood supply from the superior and inferior vena cava via the right heart. In addition, this circuit is influenced by intrathoracic pressure. Normally during inspiration, blood is transiently shunted to this circuit with no untoward effects. However, with obstructed inspirations, severe negative pressure surges develop. Pulmonary vascular pooling and pulmonary hypertension (PH) occur, leaving less blood for the left heart to pump (thus, even more hypotension and reduced organ perfusion). Pulmonary edema (fluid in the alveolar air spaces) and vascular congestion (engorged pulmonary vessels) would both develop if DS persists (as DCC), potentially explaining the "wet, heavy lungs" seen at autopsy in SIDS.

Putative Esophageal Clamping at the Diaphragm

- The other organ that traverses through the diaphragm is the esophagus. It too can become effectively squeezed or completely occluded from hypertonicity or excitation (e.g. DS, flutter, putative DCC). Consequently, gastrointestinal symptoms could arise. Indeed, reports of diaphragm flutter revealed epigastric (and chest) pain, pulsations, hiccups, belching, retching, nausea/vomiting and gastroesophageal acid reflux (GERD). Interestingly, there is an increased incidence of GERD in preterm infants with HE, as well as in adults with sleep apnea. In the latter, GERD symptoms improved with CPAP (but was never explained). This could have occurred because of a reduced diaphragmatic workload with CPAP and subsequently less diaphragm fatigue and potential for DS. Similar gastrointestinal symptoms occurred in children with focal seizures [*Fogarasi et al.* 2006, 38]. Perhaps diaphragm hyperstimulation was responsible (see *DCC in Seizure Deaths* below).

Epigastric "butterflies", the commonly experienced anxiety-provoked sensation of a transient wave-like motion in the upper abdomen, could be due to diaphragm excitation. This would suggest a connection between mind and body through the diaphragm.

- At SIDS, SUDC and SUDEP autopsy, stomach contents are sometimes found in the upper airways and mouth. We hypothesized it was caused by postmortem release of a putative esophageal clamp. As we know from the autopsy evidence in agonal obstruction — severe nITP causing intrathoracic organ injuries and petechiae — then there must have been equally elevated intra-abdominal pressures, thus providing the force behind the gastric expulsion.

Putative Compression of IVC and Aorta by Diaphragm Spasm

- In a baby with a 60 s cyanotic HE seen in **Fig. 5** below (cyan ellipse) marked by a sudden change in respirations (blue rectangle), there was a rise in arterial blood (systemic) pressure (black ellipse and arrow) [14]. Although D-EMG and gastric pressures were not available to confirm it, we hypothesized DS was responsible, by compression of the aorta at its diaphragmatic hiatus (causing increasing vascular resistance). With simultaneous nITP surges from DS airway obstruction, both caused the pulmonary blood pressure to increase as well (pulmonary hypertension, PH, green

ellipse). Because the entire event was brief and the baby survived (oxygen saturations returned to normal), DS was favored over DCC. Had excitation lasted longer, as DCC, we believe critical hypoxemia, hypotension and cardiac arrest would have occurred (consistent with SIDS).

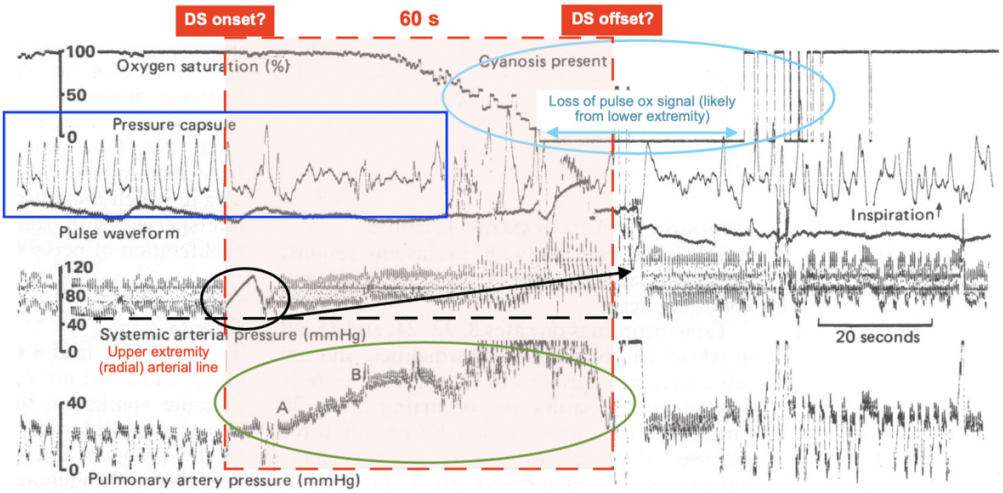


Fig. 5: A cyanotic HE in an infant with sudden-onset systemic and pulmonary hypertension. Spontaneous DS is proposed to start the episode (red shaded box), associated with disordered breathing (sudden hypopneas seen in blue box). There is an abrupt spike and quick drop in arterial blood pressure (black circle) which then escalates until the end of the DS episode (black arrow). The initial loss of signal quality at the wrist may have been from the immediate effect of DS-aortic clamping. Similarly, loss of the oxygen saturation signal (likely measured in a leg) probably occurred from a lack of blood pressure and adequate perfusion to the legs, which are subject to the most severe drop because they are below the diaphragm. Once DS resolved, breathing and all other parameters returned to normal.

- In this same study of 51 children with cyanotic HE, 76% were otherwise healthy and most outgrew them, but 8 (16%) died suddenly and unexpectedly "consistent with SIDS" (per authors).
- D-EMG and gastric pressure changes associated with a HE were reported by the same group in **Fig. 6**. It demonstrated how bursts of abnormal diaphragm contractions are associated with time-equivalent esophageal pressure changes and abnormal grunting ventilations (along with tachycardia, systemic hypertension, mild oxygen desaturations). Again, it is important to note that although hypertension occurred during this brief HE, hypotension and shock would likely have developed if sustained.

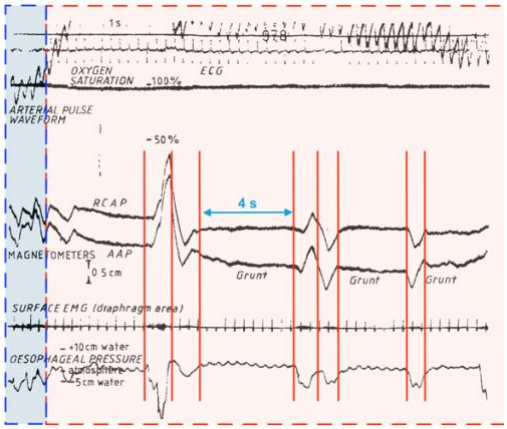


Fig. 6: A mild HE and ventilatory changes in an infant with abnormal diaphragm electrical activity and esophageal pressure swings. This ties high-amplitude bursts of diaphragm activity ("SURFACE EMG diaphragm area") to abnormal respirations, including bradypnea and 3 hyperpneas followed by brief apneas (3-4 s each) with grunting (although inspiration does not occur during the apnea, the baby can still exhale). It also ties the D-EMG activity to abnormal esophageal pressure changes. Normally with a diaphragm contraction in inspiration, there is a small negative deflection in esophageal (or gastric) pressure (seen here as low amplitude flutter-like waves between the apneas). However, these are unusually deep, wide deflections (thus explaining the ventilatory changes). The episode begins after normal tidal breathing is interrupted (from the blue- to red-shaded areas) and associated with a sudden increase in heart rate and blood pressure along with a mild, sustained oxygen desaturation. The abnormal diaphragm activity could be from repeated spontaneous DS.

Grunting and short respiratory pauses (apneas) in a young infant may indicate diaphragm spasms are occurring, and that respiratory failure is imminent (especially in males). The baby should be seen by a doctor immediately.

Complications of Repeated Hypoxemic Episodes from Diaphragm Spasms

Repeated sleep-DS-induced hypotension, venous congestion and HE in vulnerable infants are responsible for complications of prematurity, including:

- Bowel ischemia, infections and perforations (causing necrotizing enterocolitis)
- Progressive ocular hypoxia-ischemia damage to the small fragile blood vessels of the eyes (causing retinopathy and visual impairments)
- Progressive injuries to the brain [periventricular leukomalacia, white matter injury and intraventricular hemorrhages, when located adjacent to the brain cavities (ventricles)]
- Cerebral palsy [37], ADD/ADHD [18] and autism [38], all of which are associated with hypoxemic brain injury.

Recurrent DS-HE in children and adults with RI and OSA, respectively, are proposed to be triggered several times each night by REM sleep and occur over a lifetime if undiagnosed. Although the brief hypoxemia and hemodynamic abnormalities may be tolerated acutely, cumulative strain and damage of end-organs may occur over the long term, especially the heart, lungs and brain. For example:

- Recurrent episodic blood pressure surges from PH in young children would strain the heart regularly, leading to reversible wall dilatations and valve strain at first. By later childhood, continued episodes would cause right-sided cardiomyopathies (e.g. dilated, hypertrophic) and chronic PH.
- If continued into adulthood, untreated OSA would lead to hypertension, congestive heart failure and coronary artery disease (heart attacks) amongst other cardiovascular disorders. This combination also increases the risk for heart arrhythmias, some of which can be malignant, causing sudden unexpected "cardiac" deaths.
- Recurrent episodes of reduced venous drainage of the legs would increase the risk for deep blood clots, some of which can travel to the lungs resulting in pulmonary embolism, an emergency.
- All these conditions are more common in those with OSA.

- **Table 3** shows the complete spectrum of complications from DHD across all ages and this includes sudden unexpected deaths, RI in infants and OSA in children and adults.

Diaphragm Hyperexcitable Disorders & Complications in All Ages

Diaphragm hypertonicity (DH): Acute, subacute or chronic	**Diaphragm myoclonus (DM) and spasm (DS)**: Acute and transient	**Diaphragm flutter (DF)**: Acute and fleeting or sustained	**Diaphragm cramp-contracture (DCC)**: Acute and sustained

Presentations of DHD (all ages)	Resulting Pathologies	Complications in Infants	Complications in Older Children and Adults
• DS apneas and hypopneas (worse in preterms and during sleep in all ages) • DS forced expirations (infants) • DM/DF dyspnea, chest pain, epigastric pulsations (all ages) • DCC respiratory arrest (all ages)	• Reduced lung alveolar ventilation (all ages) • Systemic hypoxemia (all ages) -DS: transient but recurrent with progressive complications over short and long term -DCC: life-threatening (critical)	• Hypoxemic episodes (recurrent) with variable pallor/cyanosis, silent squirming and kicking, hiccups, hypotonia, seizure, syncope, cardiac arrest • Sleep fragmentation (arousals, pain?) • Acute lactic and respiratory acidosis • Acute electrolyte disorders • Acute bacterial infections and sepsis • Acute injuries to lungs (BPD, RDS), brain (PVL) and bowel (NEC) • Hearing and vision deficits (retinopathy) • SIDS (DCC)	• Sleep-disordered breathing ("OSA") with recurrent nocturnal hypoxemic episodes • Neurodevelopmental: cerebral palsy?, ADD/ADHD?, autism? (children) • Vascular dementia? (adults) • Atherosclerosis, cardiomyopathies, CHF, CAD, cardiac arrhythmias • SUDC, SUDEP, SCD (all from DCC)
• Aortic clamping (occlusion) at diaphragmatic hiatus causing: -brief hypertension, then -increased afterload and reduced cardiac output, then -hypotension and shock (when combined with IVC clamping)	• Blood pressure and oxygen saturation discrepancies (upper vs. lower extremities) • Organ and limb ischemia (reduced arterial perfusion) • Systemic and localized lactic acidosis (peri-diaphragmatic)		
• IVC clamping (occlusion) at diaphragmatic hiatus causing: -reduced preload and cardiac output -elevated venous pressures and venous stasis	As above, plus • Sustained hypotension • Raised ICP • Organ and limb congestion	• Pulmonary and cerebral edema/congestion • Congested/heavy thymus, liver, spleen and kidneys • Ocular: retinopathy of prematurity, blindness	• DVT, VTE, PE, ischemic stroke (paradoxical embolus) • Elevated ICP headaches • Ocular: retinopathies, central vein occlusion, macular edema, chemosis, glaucoma, proptosis
• Airway obstruction-induced nITP surges (plus hypoxemia and aortic/IVC occlusions)	As above, plus • Pulmonary hypertension • Bradycardia (inverse *Valsalva* or *Müller's* maneuver)	• Brain, lung, liver, kidney and vascular injuries as above • NCPE ("flash" pulmonary edema), right-sided heart failure • Cardiomyopathies, valvulopathies, PDA, arrhythmias	
• Systemic blood pressure swings	• Catecholamine surges • Repeated hypertension • Repeated hypotension	• Intraventricular (brain) hemorrhages, neurological disabilities • Hypertensive episodes	• Hypertension, atherosclerosis, CAD (myocardial infarction), Takotsubo cardiomyopathy, CHF, headaches, hemorrhagic strokes
• Esophageal clamping (compression) at diaphragmatic hiatus	• Physical compression at esophagus/fundus -sustained with DH, DCC -intermittent with DS, DM -rhythmic in DF	• Hiccups, chest/epigastric pain, fullness & pulsations, gastric reflux, nausea, vomiting, belching, retching • DCC: postmortem clamp relaxation → gastric contents expulsion • Epigastric aura (in seizure-induced diaphragm hyperstimulation)	

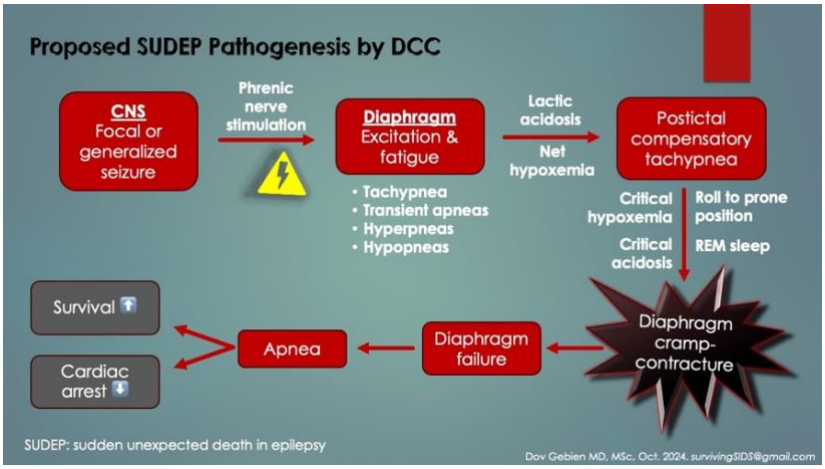
ADD/ADHD: attention deficit (hyperactivity) disorder, BPD: bronchopulmonary dysplasia, CAD: coronary artery disease, CHF: congestive heart failure, CP: cerebral palsy, DVT: deep venous thrombosis, ICP: intracranial pressure, IVC: inferior vena cava, NCPE: noncardiogenic pulmonary edema, NEC: necrotizing enterocolitis, nITP: negative intrathoracic pressure, OSA: obstructive sleep apnea, PDA: patent ductus arteriosus, PE: pulmonary embolism, PVL: periventricular leukomalacia, RDS: respiratory distress syndrome (infants), SCD: sudden cardiac death (adults), SIDS: sudden infant death syndrome, SUDC: sudden unexplained death in children, SUDEP: sudden unexpected death in epilepsy, VTE: venous thromboembolism

Table 3: Pathomechanisms and complications of diaphragm hyperexcitation disorders (DHD) in all ages. Pathological contractions occur when a ventilatory workload is added to a critically fatigued diaphragm (typically during REM sleep). They tend to be recurrent, happening many times over a single night let alone over a lifetime, with cumulative organ damage (e.g. brain, heart, lungs and vasculature). Premature, younger infants are at highest risk of DHD because of incompletely developed respiratory muscles that are prone to fatigue and overload. Fortunately, by six weeks' postnatal age, most outgrow the severest of DHD consequences (DS-induced recurrent hypoxemic episodes). However, some persist into adulthood (DS, as an OSA mimic, for example). Novel pathological mechanisms are thought to arise from the unique combination of diaphragm hypercontraction and its 4-dimensional anatomy (3D + time-based compression variations, depending on DHD type). The organ has three major structures passing through it at their diaphragmatic hiatuses (apertures): aorta, IVC and esophagus, each with a unique set of "downstream" pathological consequences and clinical presentations. Furthermore, when the hypercontracted diaphragm is inactivated by DHD, it resists independent intercostal muscle contractions to breathe, causing negative intrathoracic pressure surges. This simultaneously adds another pathological mechanism to the ongoing hypoxemia, ischemia and venous congestion. Finally, while all DHDs share the same pathological mechanisms shown here, it is their durations that differ. For example, whereas the hypoxemia or pulmonary hypertension of DS are brief and episodic, they are sustained (and life-threatening) in DCC. Ensuing cardiac strain in DS pulmonary hypertension is acute and recovers at first (is benign), but when recurrent over many months or years from repeated DS, could develop into chronic cardiomyopathies (and chronic pulmonary hypertension).

DCC in Seizure Deaths (SUDEP)

- SUDEP refers to a sudden, unexpected death of a person with epilepsy, without a clear cause found on autopsy. It typically occurs during sleep or shortly after a seizure. Although it can happen at any age, young adults aged 20-40 are most commonly affected, demonstrating a male preponderance.
- There are many shared autopsy findings between SIDS, SUDC and SUDEP, suggesting a common mechanism. We believe it to be DCC, however, the pathological sequence of events in seizure leading up to diaphragm failure differs to those already discussed.

Seizure activity from the CNS can be transmitted to the diaphragm by the phrenic nerve(s), causing diaphragm hyperstimulation (and subsequent fatigue). The hyperstimulation might induce respiratory arrest immediately or in delayed fashion, after a brief period when there is escalating lactic acidosis and hypoxemia. This creates critical diaphragm fatigue whereby postictal REM sleep, tachypnea or even a roll to prone position suddenly triggers DCC.



- Best supporting evidence for DCC in SUDEP came from three sources:
    1. In forensic autopsies comparing 13 SUDEP cases and 31 non-SUDEP sudden deaths in those with a history of epilepsy, the primary mechanism of death was asphyxia in the SUDEP group versus cardiopulmonary failure in non-SUDEP [39]. The SUDEP group was younger, more cases had an uncertain etiology of epilepsy* and were found in prone position. They also had more cardiac lesions and pulmonary congestion and edema at death. We believed that fatal DCC with obstruction was responsible. [*Perhaps DS hypoxemia is an unrecognized seizure mechanism in epilepsy.]
    2. In 100 children with 514 videotaped focal seizures, mostly stemming from the temporal lobe which is involved in volitional (nonspontaneous) breathing, a multitude of periictal respiratory and gastrointestinal symptoms were experienced. These included hyperpneas, apneas and bradypneas as well as hiccups, belching, nausea/vomiting and "epigastric aura" [40]. Epigastric (or visceral) aura is a symptom complex of short duration involving ictal abdominal discomfort, nausea and/or a burning sensation. It occurs most often with temporal lobe seizures

and receives unusual descriptions such as "*fluttering*, pressure and rolling or turning of internal organs". The gastrointestinal symptoms could all be explained by the physical effect of seizure-induced diaphragm tone/contractions on the esophagus and stomach, whereas the respiratory symptoms from diaphragm tone/contractions, overload, excitation and delayed resetting (causing bradypneas).

3. Using D-EMG in mice, experimental seizures induced immediate respiratory arrests (terminal apneas) by sustained (tonic) periictal diaphragm contractions [41]. Deaths occurred not immediately (not periictal), but rather when the apnea persisted into the postictal period.

Winding Injuries and Diaphragm Excitation

- This has partly been discussed above. In addition, like the tympanic membrane of the ear, the diaphragm serves as a hermetic seal between two anatomic compartments held under different air pressures (chest and abdominal cavities) (**Fig. 7**). A pressure increase in one causes a decrease in the other, and vice-versa, with the diaphragm buffering between extremes.

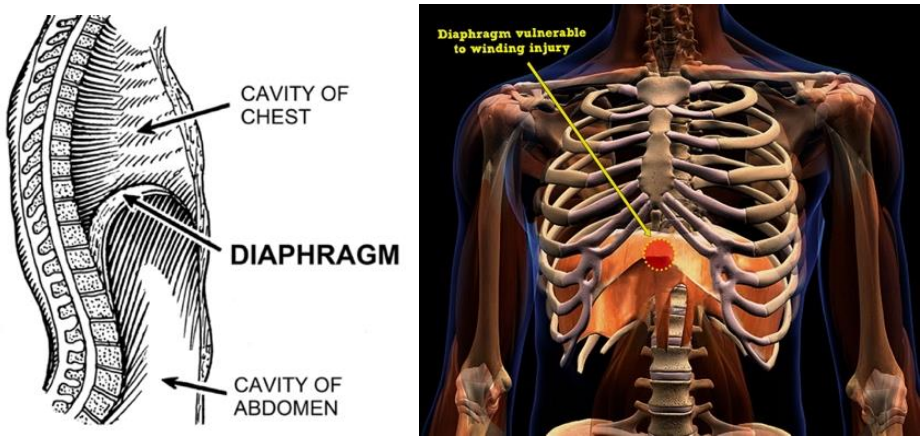


Fig. 7 Left- The respiratory diaphragm, a hermetic seal like the tympanic membrane of the ear, separates the chest from the abdominal cavity. A blunt blow to one is transmitted through the membrane to the other, sometimes causing rupture. With less severe forces, neuromuscular excitation of the diaphragm is thought to occur in the form of transient diaphragm spasm or persistent cramp (winding injuries). **Right**- The diaphragm is vulnerable to injury because of close proximity to the unprotected upper abdomen. *Source:* Pearson Scott Foresman, Public domain, via Wikimedia Commons, 2008.

- The tympanic membrane can tear from extreme air pressure changes, like SCUBA diving barotrauma. Similarly, the diaphragm can rupture from significant internal air pressure changes caused by *high velocity* impacts to the abdomen or chest, typically, motor vehicle collisions and falls from significant heights.
- Being "winded" (celiac or solar plexus syndrome) occurs by a relatively *low velocity*, non-penetrating blow to the epigastrium/chest, causing pain, forced expiration and apnea. For example, from bodily collisions, a punch or kick to the epigastrium (or blow by a hockey stick or baseball bat) or perhaps a slip and fall onto the back. Anyone who has experienced this has probably learned to protect themselves from reexperiencing the duress, by flexing their abdominal muscles in anticipation of a strike (to absorb some of the force). Also, instead of the widely held notion of

celiac plexus stimulation causing symptoms, it is rather thought to be primary (i.e. organ automaticity) given the posterior location of the plexus, protected from impacts.

The kinetic force of low velocity blunt abdominal/chest trauma is transmitted to the diaphragm, triggering neuromuscular excitation in the form of brief spasms ("traumatic DS", **t-DS**) or prolonged cramp ("traumatic DCC", **t-DCC**). The latter occurs in higher energy impacts. Apnea occurs in both, and duration dictates symptoms and survivability based on degree of subsequent hypoxemia and potential for cardiac arrest. Syncope and collapse may precede cardiac arrest (Damar Hamlin collapse). If death occurs, it would be ruled a "traumatic cardiac arrest", thus missing the primary respiratory etiology.

- The concern in t-DS is not the pain nor involuntary forced expiration, but rather the involuntary apnea that persists for an uncomfortable few seconds. Unfortunately, although t-DS has been reported in the literature to be the mechanism, supporting evidence was not provided [7]. Evidence for the t-DCC mechanism was unavailable too, primarily because of a lack of experimental studies and inherent limitations of observational case reports in fatal cases [*Maron et al.* 1995]. Again, because of the reversible nature of diaphragm excitation, it does not subsist at autopsy. As well, many sudden deaths (and football player collapses) from blunt bodily impacts have been classified as commotio cordis despite lacking two important criteria needed to establish this diagnosis.
- **Commotio cordis** (**CC**) is defined as sudden cardiac arrest resulting from a non-penetrating impact to the chest wall (which overlaps with t-DS/DCC), but typically by *a projectile* like a hockey puck or baseball. When timed to a specific phase of the cardiac cycle (during relaxation), it can induce a fatal ventricular arrhythmia: ventricular fibrillation (**VFib**) [or ventricular tachycardia (**VT**)], which is the ultimate cause of the collapse. However, in the defining experimental animal models of CC, it was reproduced by a focal blow *over the heart* and no other chest region [*Link et al* (1998)].

Not all cardiopulmonary arrests from bodily impacts are due to commotio cordis. They may also be caused by t-DCC respiratory arrest, which might have been the case in the Damar Hamlin collapse.

- As opposed to the focal aspect of CC, *non-focal* (blunt) impacts to the chest or epigastrium causing t-DCC respiratory arrest can also induce syncope/collapse and death (by secondary cardiac arrest rather than primary cardiac arrest). Severe hypoxemia may ultimately lead to the same ventricular arrhythmias seen in CC (VFib or VT), thus mimicking CC. However, there is an important difference, and this translates to prognosis…
- CPR priorities differ in collapses from CC and t-DCC because of divergent primary issues:
  - t-DCC respiratory arrest: Airway opening and rescue Breaths (A-B)
  - CC cardiac arrest: Chest compressions and Defibrillation (C-D)
  - This might improve the currently dismal success rate of CPR in traumatic arrests.
- Poor survival (and outcome) occurs in collapses from CC, historically, as low as 10% despite immediately available life-saving measures (e.g. paramedic CPR at competitive sporting events, bystander CPR at others). Although survival has improved since the 1990s, perhaps due to increased availability of portable automated external defibrillators allowing more time to get to the ER, the poor survival could be due to refractory VFib, coronary artery vasospasm, myocardial contusion or inadequate management of the patient's airway and breathing.

- It is also important to note that the respiratory arrest of t-DCC would not be obvious to bystanders because of complete airway obstruction. Inspiration does not occur and so it would be silent.
- An issue constantly plaguing bystander CPR is the lack of will to initiate mouth-to-mouth rescue breaths (fear of communicable infections, particularly so when the victim is not a child). Also, even if they are attempted, most are done incorrectly (needs a seal and to ensure chest rise with each rescue breath). In addition, this important recommendation apparently went missing since the arrival of the 2005 CPR guidelines.
- As such, it may only be once the victim is in the ER when the airway is finally managed properly. But even then, the added airway resistance of DCC requires harder squeezing of bag-mask ventilations, something feared by healthcare providers because of potential lung overinflation injury.
    - Reports of added airway resistance on initial ventilatory efforts were made by Southall [14] and others, as well as this writer's experience as an ER physician and discussions with neonatologists. It may have been due to the hypercontracted state of DS/DCC. If higher bagging forces are initially used to overcome it, survivability may improve.

Improved survival in traumatic and spontaneous DCC cardiopulmonary arrests may occur with improved rescuer management of the airway and breathing (by both lay public and healthcare provider). This involves overcoming the added airway resistance initially and then visually confirming chest rise with each rescue breath delivered.

Diagnosing Diaphragm Fatigue and Excitation

- From frequent hiccups and RI in neonates (i.e. apneas-hypopneas, periodic breathing, HE) to bronchiolitis, apneas, breath-holding spells and life-threatening symptoms in older babies and young children, the various etiologies and parameters of underlying diaphragm fatigue and excitation can be evaluated.
- **Objective signs of diaphragm fatigue are the same as those of "respiratory insufficiency"**, a term commonly used in the emergency room to describe ventilatory distress. But instead of focusing just on the lungs, consideration should also be made to the respiratory muscles. Signs in infants include labored breathing, tachypnea, nasal flaring, grunting, wheezing, sweating, pallor/cyanosis, rib retractions and hiccups. Sleepiness and paradoxic breathing are very serious findings. Signs in adults are similar, including preference for sitting upright and sudden confusion or sleepiness.
- **Signs of DS and DF** overlap, however, some are specific to flutter. *DS and DF:* recurrent or prolonged apneas, desaturations, tachypnea, hypoventilations, bradycardia, rib retractions, paradoxic breathing, cyanosis, pallor, hypotonia, syncope, seizure, unexplained events, frequent hiccups. *DF:* epigastric pulsations, ratchet-like inspirations and fluttering, murmur asynchronous with heart, friction rub, sense of impending doom.
- **ECG**: Sinus tachycardia, bradycardia, intermittent ST repolarization abnormalities, T-wave notches and inversions. Avoid dismissing artifacts as body movements; excitation could be responsible.

- **Lab testing** (**Table 4**) can assess for the causes and outcomes of diaphragm fatigue and excitation, primarily DS and DF. The former includes anemia (a cause of life-threatening apneas and other RI in preterm infants) *[Poets et al. 1992]*, magnesium deficiency and other electrolyte disorders *[Caddell 2001]* and abnormal blood acid-base balance (metabolic acidosis and alkalosis) [12]. The latter includes screening tests to reveal diaphragm damage from hypoxia, hyperthermia, myopathic viral infections and/or resistive loading include serum creatine kinase (CK or CK-MM, muscle type) and skeletal muscle troponin-I (STnI). Although not specific to respiratory muscles, correlating levels to changes in clinical state would be helpful. In infants with bronchiolitis, high CK levels could screen those at higher risk for respiratory distress and sudden apneas. This alone would not only save lives from SIDS but also reduce the flu/RSV season annual burden on health care systems, translating to reduced costs and waiting times (and satisfied parents).

Suggested Labs Tests (screening, trends and respiratory distress PRN)
Nasopharyngeal swab (r/o respiratory viruses)
Hemoglobin (r/o anemia)
BUN/creatinine ratio, serum osmolality (r/o hypovolemia)
Extended electrolytes (sodium, potassium, calcium, magnesium, phosphate)
Lactate and VBG (pH, pCO_2, HCO_3)
Nicotine and metabolites (r/o absorption from tobacco smoke).
CK-MM or sTnI (correlate with VBG and respiratory distress PRN)

PRN: Pro re nata (as necessary), r/o: rule out, VBG: venous blood gas, CK-MM: creatine kinase muscle fraction, sTnI: *fast isoform* skeletal muscle troponin-I. CK-MM may be elevated in DS, DF, RF, DCC and even from the hypertonicity of diaphragm fatigue.

Table 4: Proposed labs and biomarkers revealing evidence of diaphragm fatigue, excitation and myopathy.

- **Other investigations** (**Table 5**) to evaluate for active diaphragm excitation (DS, DF, RF) include diaphragm ultrasound and EMG along with RIP. Together, these might determine if the diaphragm is contracting independently (automaticity) or by neural stimulation.

Suggested Investigations (monitoring and active excitation PRN, histology)
Continuous RIP and transcutaneous/esophageal D-EMG in high-risk individuals*
Bedside abdominal US and D-CEUS (perfusion) in suspected active DHD†
4D CT (rapid sequence of images) in suspected active DHD†
Cine MRI (rapid sequence of images) in suspected active DHD†
Bedside fluoroscopy (C-arm) or dynamic chest radiography in active DHD†
Diaphragm biopsy (r/o myofiber disruptions, inflammation, contraction bands, fibrous scars)

RIP: respiratory inductive plethysmography, D-EMG: diaphragm electromyography, US: ultrasound, D-CEUS: diaphragm contrast-enhanced ultrasound, DHD: diaphragm hyperexcitation disorders († DS, DF, RF or near-DCC). * Those in respiratory distress or have lab abnormality or SIDS sibling(s).

Table 5: Proposed monitoring and imaging revealing evidence of diaphragm fatigue, excitation and myopathy.

Treatment Options

- **Table 6** provides emergent interventions and potential medications identified on preliminary literature review that *might* improve diaphragm fatigue and thus prevent or attenuate excitation. In patients of any age with respiratory distress, this includes correcting anemia, electrolyte disorders and acidosis as well as providing supplemental oxygen, rehydration and antipyretics as needed.
- Methylxanthines such as caffeine and theophylline have been used for over 50 years to reduce apneas-hypopneas and HE in infants. They are thought to stimulate the CNS respiratory centers; however, also have peripheral effects on respiratory muscles. Chlorpromazine, an older antipsychotic with relaxation effects on the CNS and skeletal muscles, was most commonly used to treat DHD, particularly effective in intractable hiccups and RF. Its calming effect might even reduce diaphragmatic hypertonicity in extreme anxiety. N-acetylcysteine has shown promise by improving diaphragm force generating capacity and anti-inflammatory activity in a mouse model of muscular dystrophy. Vitamin E, an antioxidant, reduced muscle fiber damage, oxidative stress and inflammation in test animals. Creatine, a high-energy phosphate source in muscle, enhanced protein synthesis and muscle function. Finally, diaphragm pacing might treat or prevent unstable DHD.
- Treatment is a high priority in OSA because of its ubiquity and very serious comorbidities. However, despite the use of CPAP improving OSA severity in adults, long-term benefits such as reduced hypertension were minimal. Instituting therapies tailored to reducing respiratory fatigue and workload in OSA offers a novel approach.

Emergent Interventions for Diaphragm Distress	Example Medications
Supplemental oxygen	Caffeine, theophylline
Intravenous access	Chlorpromazine, haloperidol
Cardiac monitor, RIP, pulse oximetry, capnometry	Carbamazepine, phenytoin
CPAP, nasal mask or intubation/MV	Gabapentin, pregabalin
Minimize psychiatric stressors and pain	SSRIs
Stop antireflux medications	Cyclobenzaprine
Anticonvulsant medications PRN seizure	Benzodiazepines
Treat bronchospasm (β-agonists, theophylline?)	ACE inhibitors
Correct hypovolemia and acidosis (bicarbonate?)	Calcium channel blockers
Correct anemia and electrolyte disorders	β-agonists, sympathomimetics
Treat infection (antibiotics, antivirals?)	Erythropoietin
Body cooling measures PRN	N-acetylcysteine
Diaphragm or phrenic nerve pacing?	Vitamin E (α-tocopherol)
	Creatine

RIP: respiratory inductive plethysmography, CPAP: continuous positive airway pressure; PRN: pro re nata (as necessary); SSRIs: selective serotonin reuptake inhibitors, ACE: angiotensin-converting enzyme.

Table 6: Preliminary list of interventions and medications that may improve diaphragm fatigue and reduce subsequent HE. All medications were found on broad literature review and have not been tested or confirmed. *They are here for demonstrative purposes only.*

Conclusions [return to text]

- It is exceptional the wealth of novel medical insights that stemmed from a solitary patient, let alone just two symptoms (bearhug pain apneas) that woke him from sleep sporadically throughout his childhood and youth. Each episode caused a near-death experience from inspiratory arrest.
- Logical reasoning led us to speculate that novel diaphragm cramp-contracture (DCC) was most likely responsible (a completely new diagnosis). Neuromuscular excitation of the diaphragm (cramp) had caused acute diaphragm failure (apnea by contracture). Like limb cramps, it is probably triggered by work overload of a fatigued muscle.
- In sleep-related diaphragm arrests (prolonged apneas), diaphragm overload is thought to primarily occur by REM sleep inhibition of upper airway-dilating or accessory inspiratory muscles. This appears spontaneously, and its unpredictability combined with internal location of the diaphragm make it difficult, if not impossible to observe. Alternatively, a body roll to prone (face-down) position or sudden increase in respiratory rate can overload the diaphragm.
- Surprisingly, aside from hiccups, a variety of "diaphragm hyperexcitability disorders" had already been reported in all ages, such as diaphragm spasm, flutter and myoclonus. Spontaneous and traumatic forms of diaphragm spasm existed, both exhibiting forced expirations and involuntary apneas and hypopneas. When spasms are brief, transient hypoxemic episodes may occur, and the patient generally recovers. However, when sustained, respiratory arrest and critical hypoxemia could ensue. Death would be rapid and silent (inspiratory arrest). This could explain some sudden unexpected deaths, including SIDS and unexplained deaths in older children (SUDC) as well as sudden cardiac arrests, even those from severe abdominal winding injury (i.e. kinetic energy diaphragm excitation).
- Neuromuscular blockade by succinylcholine and nicotine also induce excitation in skeletal muscles of the limbs and diaphragm. Early twitches (fasciculations) are followed by paralysis from muscle contracture. In nicotine overdose, deaths occur rapidly from respiratory paralysis. This overlaps with the proposed pathogenesis of DCC and might be the operative pathologic mechanism in SIDS cases where infants are exposed to tobacco smoke. For this reason it is clear nicotine is exceptionally dangerous.
- The causes of diaphragm fatigue are numerous. Young infants are especially vulnerable because of higher ventilatory workloads and underdeveloped, weaker inspiratory muscles (particularly males). We speculated SUDC was less common than SIDS because maturation of respiratory muscles protects the child from critical diaphragm fatigue and neuromuscular overload.
- DCC was also proposed to cause some epilepsy deaths (SUDEP), whereby seizure activity carried by the phrenic nerves induce diaphragm hyperexcitation and work overload, culminating in terminal apnea. This was supported by shared autopsy findings among SIDS, SUDC and SUDEP.
- Breathing issues in preterm infants (e.g. forced expirations, apneas-hypopneas, hypoxemic episodes and periodic breathing), as well as sleep-disordered breathing at all other ages (e.g. OSA), may be caused by spontaneous diaphragm spasms in addition to CNS dysfunction or abdominal muscle contractions (in infants). EMG evidence of diaphragm fatigue [*Lopes et al. 1981*] and intermittent bursts of abdominal *surface* electrical activity likely from the diaphragm [19,23] provided the best support. Thus, "peripheral

apneas" (respiratory muscle dysfunction) need to be taken into consideration as a cause of hypoxemic episodes in sleep-disordered breathing in all ages.

- Compelling evidence at SIDS autopsy: diaphragm histology revealed an anoxic "hypercontraction injury" characteristic of DCC as well as myofiber disruptions consistent with viral myositis, hyperthermia and inspiratory muscle overloading. Along with critical acidosis and hyperkalemia in SIDS, all require further investigation. **Autopsy protocols in SIDS and other sudden unexpected deaths should include diaphragm histology, pH, lactate and electrolyte levels**.
- Increased diaphragmatic muscle tone in acute anxiety might link physical and psychological states at the diaphragm, potentially explaining "stomach butterflies" and other stress-related gastrointestinal symptoms.
- Incredulously, *thumb-sucking may have spared Patient 0's infant life* by delaying the onset of DCC (it started only after he ceased the habit at age 7). This suggests digit-sucking (and pacifiers) might reduce diaphragmatic workload or prevent ventilatory pausing at end-expiration, aligning with their known SIDS-preventive effects.
- Although the evidence supporting DCC presented here is compelling, it is still indirect. **Reproducing DCC in lab and validating its existence in vivo are urgently needed**.

The Patient's Perspective and supplementary tables, figures and videos are provided in the appendix below.

APPENDIX

Supplemental Table S1 [return to text]

Differential diagnosis of Patient 0's symptoms. Causes of pediatric rib pain (A) and apnea (B) are listed separately and combined (C). Conditions for inclusion in (C), as suggested by the patient's history, were recurrent nocturnal spontaneous sudden onset cramp-like bilateral rib (bearhug) pain with inspiratory arrest. Clinical reasoning yielded six final diagnoses of varying clinical confidence.

A. Unilateral and Bilateral Pediatric Rib Pain*		**Apnea?**	**Recurrent?†**
	Rib fracture, muscle strain, intercostal neuralgia	No	Possible
	Fibromyalgia, juvenile rheumatoid arthritis	No	Possible
	Pleurisy, pleurodynia	No	Possible
	Tumours of chest wall and ribs	No	Unlikely
	Pneumothorax, pneumomediastinum	No	Unlikely
	Electrical injury	**Possible**	**Possible**
	Panic attack, somatoform and fictitious disorders, malingering	**Possible**	**Possible**
	Child abuse	**Possible**	**Possible**
	Intercostal muscle cramp(s)	**Possible**	**Possible**
	Diaphragm cramp-contracture	**Possible**	**Possible**
B. Pediatric Apnea*		**Rib Pain?**	**Recurrent?†**
Mechanical	Obstructive sleep apnea	No	Yes
	Upper airway trauma, burns, foreign body	No	Unlikely
	Airway tumour, polyps, bilateral vocal cord paralysis	No	Unlikely
	Tonsillar hypertrophy, tracheal webs & atresia, macroglossia	No	Unlikely
	Epiglottitis, abscess, croup	No	Unlikely
	Anaphylaxis	No	Possible
	Intercostal muscle cramp	**Yes**	**Possible**
	Diaphragm cramp-contracture	**Yes**	**Possible**
Nervous system	Seizure	Unlikely	Yes
	Cardiac arrhythmia	No	Possible
	Medications (opioids, neuromuscular blockers)	No	Unlikely
	Toxins (botulism, tetanus, curare, tetrodotoxin)	No	Unlikely
	Exposures (carbon monoxide, cigarette smoke)	No	Possible
	Idiopathic central sleep apnea, periodic breathing, Cheyne-Stokes, obesity hypoventilation syndrome	No	Yes
	Parasomnias (sleep paralysis, night terrors)	No	Possible
	Breath-holding	No	Possible
	Panic attack, somatoform and fictitious disorders, malingering	**Possible**	**Possible**
	Child abuse	**Possible**	**Possible**
Mixed	Acid reflux with laryngospasm	No	Yes
	Upper and lower respiratory infections	No	Yes
	Aspiration pneumonia	No	Possible
	Sepsis and serious bacterial infections	No	Possible
Traumatic	Head trauma, Raised intracranial pressure	No	Unlikely
	Spinal cord injury, bilateral phrenic nerve injuries	Possible	Unlikely
	Bilateral pneumothoraces, pneumomediastinum	Yes	Unlikely
	Electrical injuries	**Possible**	**Possible**
	Diaphragmatic spasm from winding injury	**Possible**	Unlikely
C. Recurrent Bilateral Rib Pain and Apnea*†			**Clinical Confidence**
	Repeated electrical injuries		Low
	Recurrent seizures		Medium
	Panic attack, somatoform and fictitious disorders, malingering		Medium
	Child abuse		Medium
	Bilateral intercostal muscle cramps		High
	Bilateral diaphragm cramp-contracture		High

*List is inexhaustive. †"Recurrent" refers to relapsing and remitting. Bold: higher clinical suspicion, Italics: putative (unproven).

Patient's Perspective and Brief Discussion **[**return to text**]**

This account was written by Patient 0 who is a practicing medical doctor born in 1970 (53 years old on date of disclosure, 2023). With trauma counselling he had explored life-threatening breathing emergencies that had awakened him from sleep periodically throughout his childhood and youth. He feels he came within a breath of losing his life each time. It appears his memories were repressed as a defense (survival) mechanism.

"One night in bed when 7 or 8 years old, I suddenly awoke from a sharp pain in my ribs that felt like someone had picked me up from behind in a tight bearhug. The constant intensity pain radiated from back to front in a C-shaped distribution with sternal sparing. I couldn't breathe in at all and was baffled because my mouth had opened involuntarily at first when I gasped for air, like a fish out of water. This all happened in under two seconds. As I fully awoke, turning to tell the person who was bear-hugging me to stop, I was shocked to realize I was in my bed and that nobody was there. The bearhug and inability to inhale persisted.

Despite the growing sense of impending doom, I began troubleshooting. When I tried inhaling more forcefully though, it was met with equal and opposite, complete resistance to airflow. Realizing it was futile, I knew I had to *try something else*. So, then I tested to see if could still exhale. That worked and I remember telling myself not to lose all the air in my lungs, *just in case* (to conserve it, if I needed to exhale again). I still couldn't breathe in, and the pain continued. I was not panicked and did not have stridor, choking or any unusual sensation in my throat. Again, realizing I was nearing death, I knew I had to do something different.

This time I exhaled and followed it rapidly by three short-burst inhalations with pursed lips (to increase inspiratory pressure [see YouTube Video]). Immediately the pain stopped, and my breathing returned to normal. No more resistance like before. Completely gone. Crisis averted, just like that.

No fear. Not shaken up. Just surprised and mildly curious about what had happened.

And as only a seven-year-old can, despite a near-death experience and the powerful yet brief fear, I went back to sleep.

The following morning I was puzzled because the pain had all but disappeared. I had already learned from an ankle sprain that severe pain like that typically lasted days, if not longer, but this pain was gone.

Soon afterwards I noticed a pilot on TV spinning in a centrifuge using the same distinctive pursed-lip breathing. I had never seen that before. He's using *my trick*, I mused.

That was not the end of the breathing emergencies. They happened sporadically throughout the entire course of my childhood and youth, but only at night while fast asleep. I don't remember how often they occurred or if I had any associated illnesses like a cold or flu. However, I did have a fair bit of diarrhea during my childhood, and the cause was never diagnosed. Mom told me it might have had something to do with the hiatal hernia surgery when I was a baby. However, now, as a MD, I don't think that was the case (one is upper whereas the other is a lower bowel problem).

With repeated episodes over the years, I eventually recognized, in my sleep, prodromal flickering pains in my ribs [fasciculations] to be a warning sign of the impending bearhug apnea like that of the first episode. I would wake from this and take in a quick breath to prevent 'the big pain' from kicking in so I could fall back asleep quickly. I can say with absolute certainty, the pain was from a muscle cramp. Also, that if I didn't take in that breath, the bearhug would come on just at the *very end of expiration*. I can still recall how the pain always spread from a spot in my right posterolateral ribs to the encircling bearhug in a matter of milliseconds if I didn't.

The rescue breaths were so loud, I remember being awakened one night by their sound… coming from me! It appears I had grown so accustomed, that I did them in my sleep. Oddly, I also recall telling myself to *keep it quieter next time,* because I didn't want to wake anybody else up. My memory of that bedroom places it in our family's newer home, therefore, between ages 17 and 23. I'm not certain if I had any episodes after that.

There are a few notable childhood medical conditions to share.

Due to severe gastroesophageal reflux, malnourishment and failure to thrive over my first year of life, I underwent an uncomplicated open exploratory-laparotomy with Nissen fundoplication at 18-months of age.

It definitively treated a congenital hiatal hernia. I recovered well, quickly gained weight and do not recall having reflux symptoms after that.

Since age 8 or 9 years, I frequently experience painful fasciculations and muscle cramps that cause contracture-like stiffness of the affected limb(s). One day, the small muscles of the hand are affected (claw hand), whereas the next involves larger ones like a calf or posterior thigh muscle. With repeated episodes over the years, fasciculations alerted me to prevent imminent cramp by quickly stretching the muscle. I have not received a diagnosis for this ongoing condition.

In addition, beginning at roughly 10 years old, I occasionally became suddenly and extremely fatigued during prolonged, intense exercise. I learned it occurred when not eating properly beforehand. Carbohydrate-rich foods prevented and aborted symptoms. This condition was undiagnosed at the time of writing but is consistent with hypoglycemia from McArdle's (glycogen storage) disease.

Social history: I was the second male child of a Gravida 4, Para 2 cigarette smoker. Brother denied sleep-related breathing issues, bearhug pains or reflux. I slept alone in an upstairs bedroom in a household containing cigarette smoke that was heated in wintertime.

Notably, I had stopped thumb sucking around the same time as the breathing emergencies first started [*important because pacifiers are SIDS protective*]. I cannot think of anything else that might have changed which would explain why it all started at age 7 and not any sooner [*as an infant*].

In terms of childhood risk factors overlapping with SIDS, mine were numerous including male sex, reflux, chronic diarrhea, residing in a colder climate, household cigarette smoke from maternal use, nocturnal diaphoresis, deep sleeping with preference for the prone position and tendency to pull bed linens over my shoulders and head.

I do not have a history of panic attacks, anxiety, depression or sleep disorders such as obstructive sleep apnea, night terrors or sleep paralysis. No cardiac abnormalities such as palpitations, exercise intolerance or syncope. No respiratory issues such as bronchospasm, pneumonia, choking episodes or prolonged cough or colds. No allergies, anaphylaxis or unusual childhood infections. No seizures, atypical headaches or focal muscle weakness. No family history of cardiac arrhythmias or sudden unexpected deaths, including SIDS".

* * *

I survived these life-threatening events because, as opposed to an infant, I had the benefit of *wherewithal* and ability to problem solve. It is only now, upon reflection as an adult, do I realize how lucky I am to be alive.

I am determined to eradicate DCC. Sleeping children need our help!

Brief Discussion

Given such a highly detailed account, it is clear the adult physician/patient was intimately aware of all features pertaining to his childhood "bearhug pain apneas". From the cramp-like nature, it is straightforward to infer spontaneous muscle cramps were causal. Anatomical location suggests it was either the bilateral intercostal muscles or diaphragm (or both), however, since involuntary apnea occurred, the diaphragm must have been involved as it is the primary muscle of inspiration. Therefore, simultaneous spontaneous cramps of the bilateral intercostal muscles and diaphragm were proposed. Because the organ had failed (apnea occurred), the term 'diaphragm cramp-*contracture*' was applied (DCC). Upon literature review, it appeared this abnormality was completely unknown to medicine and therefore could be considered novel (see Table: *Differential Diagnosis*).

The episodic diarrhea may have caused a metabolic acidosis from bicarbonate loss. This acid-base disorder is well known to precipitate or exacerbate limb muscle cramps, particularly during exercise and when an individual is dehydrated and/or overheated. By extension, it could have contributed to diaphragm

excitation. This may have been compounded by Patient 0's history of generalized muscle cramps (possibly Cramp-Fasciculation Syndrome or some other myopathy).

By initiating *expiration* to overcome DCC (because inspiration did not), this may have restored respiratory function by forcing the diaphragm out of its hypercontracted state. This lifesaving diaphragm movement could have been augmented by the "1-2 punch-like" breathing maneuver: the rapid expiration-inspiration could have primed or recoiled the organ in the opposite direction at first, giving a mechanical advantage and moving it more forcefully out of hypercontraction.

As for why the bearhug apneas started at age 7 and not any sooner (during his infancy), something notable arose: cessation of thumb sucking. Indeed, pacifiers (dummies) were found on literature review to be SIDS-preventative [1]. *This was fascinating*: had thumb sucking protected his early life from DCC? We can only speculate this might have averted respiratory pausing at end-expiration, the point in which he related that the bearhugs were triggered. Or perhaps it simply reduced diaphragm workload (or both)? Unfortunately, no studies were found comparing respiratory flow waveforms in infants sleeping both with and without pacifiers.

1 Li DK, Willinger M, Petitti DB, Odouli R, Liu L, Hoffman HJ. Use of a dummy (pacifier) during sleep and risk of sudden infant death syndrome (SIDS): population based case-control study. *BMJ*. **2006** Jan 7;332(7532):18-22. PMID: 16339767.

Supplemental Table S2 [return to text]

Why diaphragm cramp is unknown to medicine. Speculation provided as to how DCC has evaded detection historically.

Spontaneous DCC (s-DCC): Is a proposed mechanism of spontaneous respiratory arrests in individuals with critical diaphragm fatigue thought to cause some cases of SIDS, SUDC and SCD. Sleep is an especially vulnerable time, primarily because of REM sleep inactivation of airway dilator and respiratory accessory muscles (added diaphragmatic workload). The process is rapid, with only 5-10 s before hypoxic syncope and 1-2 min before cardiac arrest ensue (however, can be aborted by rescue breaths).

Traumatic DCC (t-DCC): Is speculated to be a severe form of abdominal winding injury (celiac or solar plexus syndrome). It occurs from a heavy, non-penetrating blow to the epigastrium or chest, stunning the diaphragm and inducing respiratory arrest by a *sustained* diaphragmatic spasm (diaphragm cramp). As above, this would rapidly progress to syncope, cardiac arrest and death if not aborted. In contrast, milder impacts induce a forced expiratory apnea from *transient* diaphragm spasm, whereby the victim cannot inspire momentarily (until the diaphragm recovers).

Seizure DCC (sz-DCC): Seizure activity is proposed to hyperstimulate the diaphragm via the phrenic nerves (causing SUDEP by terminal apnea). This presents as a mixture of periictal hyperpneas, hypopneas and apneas, causing net hypoxemia (and sometimes cyanosis). This alone can trigger DCC. However, if seizure continues, lactic acidosis and critical hypoxemia will develop (both of which impair skeletal muscle contractility), and could also catalyze DCC. Additionally, a postictal roll to prone position, compensatory tachypnea or onset of REM sleep can trigger delayed-onset DCC (added diaphragm workload).

1 Historically, compared to the other vital pump (heart), the diaphragm has been grossly understudied and underappreciated as causing serious disease.

2 DCC is thought to have exceptionally high mortality (few survivors who live to talk about it). The most commonly affected age groups in s-DCC are infants and preverbal children; too young to remember (childhood amnesia). Also, nocturnal cases are triggered in REM sleep, a deep sleep stage that makes recall of events less clear. Those who survive hypoxic syncope of t-DCC will likely have retrograde amnesia, unable to recall the respiratory arrest (e.g. collapse of NFL player in 2023).

3 The process is unwitnessed in nocturnal cases, and silent because of the inspiratory arrest (victim unable to cry out for help).

4 Death from DCC respiratory arrest is rapid and mimics other conditions like choking, seizure and collapse from a sudden cardiac arrest (e.g. VFib, VTach). This would lead to misclassification of the primary cause of death. Those in fatal winding injuries would be also be misclassified as traumatic cardiac arrests or commotio cordis.

5 Excitation as diaphragm spasm or cramp is not visible because the diaphragm is internal. Specialized studies are needed. Also, excitation is difficult to capture because of its spontaneous, unpredictable and transient nature. Continuous diaphragm EMG offers the best alternative; however, spasms and cramps would then need to be filtered from electrical noise and body movement artifacts.

6 Similar to VFib and VTach of the heart, pathological excitation of diaphragm muscles do not persist postmortem (making it undetectable at autopsy). Also, the internal mechanical airway obstruction of DCC is not visible (as the offending agent is the diaphragm itself).

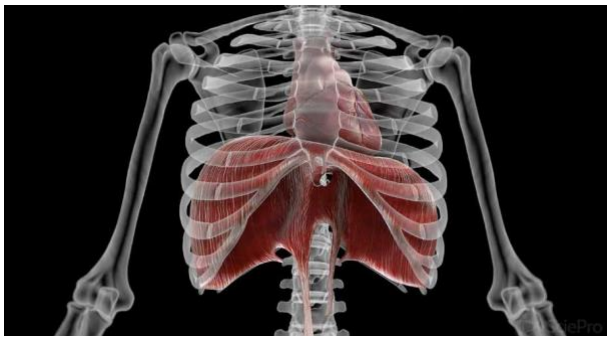
7 Gross evidence of diaphragm excitation is not visible to the naked eye. Also, current autopsy guidelines in sudden unexpected deaths omit diaphragm histology, thus, missing the myopathic changes.

8 Given DCC apnea is silent, it can go undetected at home and in non-monitored hospital inpatients. Even in patients receiving respiratory monitoring, airflow is not measured; rather chest impedance (respiratory efforts only). Because of continued chest movements in DCC (attempting to breathe against obstruction), the apnea alarm is not triggered. Also, where many false alarms occur, as is common on busy wards, apnea alarms sometimes do not receive immediate attention (as does cardiac arrest). Therefore, the apnea of DCC is being missed in all settings. Lastly, oxygen desaturation alarms are a late finding, thus missing the critical event.

DCC: diaphragm cramp-contracture, SIDS: sudden infant death syndrome, SUDC: sudden unexplained death in childhood, SCD: sudden cardiac death, SUDEP: sudden unexpected death in epilepsy, EMG: electromyography, VFib: ventricular fibrillation, VTach: ventricular tachycardia

Video S1 [return to text]

When the diaphragm contracts, it moves caudally thereby expanding ribcage and lungs. When it contracts in spasm, a variety of respiratory disorders can occur: forced expirations, apneas, hypoventilation (shallow breathing) and/or a slowed respiratory rate. Video available on YouTube.



Video S1 – Diaphragm 3D animation. Click to watch on YouTube. From *SciePro* (@SciePro .

Video S2 [return to text]

Patient 0's rescue breath technique was used to overcome the bearhug pain and inspiratory arrest of diaphragm cramp. It is possible however, that exhalation-inhalation is all that is needed. Dr. Gebien demonstrates the technique by first exhaling, then three short-burst, positive-pressure inspirations using his tongue to completely occlude the airway by percussing the hard palate. The patient had recounted how this resembled a pilot breathing in a centrifuge (preventing compression of the lungs under centripetal forces). Video available on YouTube.

Video S2 – Rescue breath technique. Click to watch on YouTube

Video S3: Playlist compiled by Gebien, Diaphragm 3D Anatomy and Damar Hamlin collision.

Video S3 – Damar Hamlin collision. This is not a normal tackle (arms splayed out). Click to watch on YouTube

Table 1 Citation List [return to text]

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