Diaphragmatic Cramp-like Spasm – A Novel Terminal Mechanism in Sudden Unexpected Deaths

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Short Title: Diaphragm Cramp in Sudden Unexpected Deaths

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Abbreviations: BDP: bilateral diaphragmatic paralysis, **CK-MM**: creatine kinase muscle type isoenzyme, **CPAP**: continuous positive airway pressure, **DCS**: diaphragmatic cramp-like spasm, **DD:** diaphragmatic dysfunction, **DF**: diaphragmatic flutter, **DP**: diaphragmatic paralysis, **EMG**: electromyogram, **RAM**: respiratory accessory muscles, **SIDS**: sudden infant death syndrome, **SUDC**: sudden unexplained death in childhood

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ABSTRACT 1 *(Structured)*

Objectives: Create a differential diagnosis for a 7-year-old male's reversible bearhug rib pain with inspiratory arrest and gasping. Determine if this could be related to SIDS.

Methods: Clinical reasoning pointed to the existence of a novel diagnosis. This prompted literature reviews on the respiratory diaphragm and sudden, unexpected deaths.

Results: Despite equal importance in maintaining life, the diaphragm has been grossly underestimated compared to the heart. Like other skeletal muscles that are prone to cramping when fatigued and overworked, diaphragm cramp is possible. Diaphragmatic paralysis (DP) induces respiratory distress when sudden, bilateral and complete. Infants, who are most affected by unexpected sudden deaths, are unable to use respiratory accessory muscles sufficiently to compensate for acute bilateral DP. Onset of REM-sleep in those with diaphragm fatigue could trigger a diaphragmatic cramp-bilateral DP-respiratory arrest cascade from work overload.

Evidence: Case reports of young infants with diaphragmatic flutter documented significant respiratory distress.

REM-sleep inactivation of accessory muscles induced apnea in some infants with diaphragmatic fatigue, some requiring mechanical ventilation.

Tobacco smoke is a well-known SIDS risk factor. In nicotine toxicity, death occurs by rapid respiratory muscle paralysis from neuromuscular block. Animal limb muscles exposed *in vitro* to nicotine exhibit contractile dysfunction (fatigue, tetanic contractures).

Autopsy studies of diaphragms in SIDS revealed contraction band necrosis in the majority, indicating lethal damage had occurred terminally from a "hypercontractile state". Pulmonary edema and intrathoracic petechiae suggestive of asphyxia are also common. Terminally generated, negative intrathoracic pressures from airway obstruction has been speculated.

Conclusion: Hypothesis: "non-cardiac sudden, unexpected death is primarily caused by respiratory arrest from 'diaphragmatic cramp-like spasm' (DCS)". If confirmed, the patient's rescue breaths should be taught to all. Top CPR priorities include maintaining airway patency and confirming chest rise with rescue breaths. Autopsies in sudden, unexpected deaths need to include diaphragm histology.

ABSTRACT 2 (*Customized*)

Background: Despite equal importance in maintaining life, the respiratory diaphragm has been grossly underestimated compared to the heart, particularly so in sudden, unexpected deaths. Like other skeletal muscles prone to cramping when fatigued and overworked, diaphragm cramp is possible. Diaphragmatic paralysis (DP) induces respiratory distress when sudden, bilateral and complete. Infants, who are most affected by unexpected sudden deaths, are unable to use respiratory accessory muscles sufficiently to compensate for acute bilateral DP. Onset of REM-sleep in those with diaphragm fatigue could trigger a diaphragmatic cramp-bilateral DP-respiratory arrest cascade from work overload.

Hypothesis: Non-cardiac, sudden unexpected death is primarily caused by "diaphragmatic cramp-like spasm" (DCS)-induced respiratory arrest.

Evidence supporting hypothesis: Case reports of young infants with diaphragmatic flutter documented significant respiratory distress.

REM-sleep inactivation of accessory muscles induced apnea in some infants with diaphragmatic fatigue, some requiring mechanical ventilation.

Tobacco smoke is a well-known SIDS risk factor. In nicotine toxicity, death occurs by rapid respiratory muscle paralysis from neuromuscular block. Animal limb muscles exposed *in vitro* to nicotine exhibit contractile dysfunction (fatigue, tetanic contractures).

Autopsy studies of diaphragms in SIDS revealed contraction band necrosis in the majority, indicating lethal damage had occurred terminally from a "hypercontractile state". Pulmonary edema and intrathoracic petechiae suggestive of asphyxia are also common. Terminally generated negative intrathoracic pressures from airway obstruction has been speculated.

Evidence against hypothesis: Infants with diaphragmatic flutter did not have apneas or associated sudden deaths.

Confirmation of hypothesis and implications: Creatine kinase levels could screen for recent cramps in infants with acute life-threatening events to select those for monitoring to detect, manage and prevent DCS. Experiments to reproduce DCS could start with delivering electrical currents to intact diaphragms. Rescue breaths should be taught to all. Maintaining a patent airway and confirming chest rise are essential CPR priorities. Autopsies in sudden, unexpected deaths need to include diaphragm histology.

Clinician's Capsule

What is known about the topic?

- The respiratory diaphragm is a grossly under-studied, life-sustaining pump of equal importance to the heart.

What did this study ask?

- What could cause spontaneous, sudden-onset, recurrent, nocturnal, cramp-like "bearhug pain" with gasping and apnea in a healthy boy?
- How did he survive? Could this be a near miss, SIDS-equivalent case?

What did this study find?

- Like fatigued skeletal muscles prone to reversible contractures, "diaphragmatic cramp-like spasm" (DCS) could cause sudden deaths by respiratory pump arrest.
- Onset of REM-sleep is the likely trigger for DCS-induced respiratory arrest.

Why does this study matter to clinicians?

- The patient's autoresuscitative rescue breath technique needs to be learned by all.
- In children presenting with acute, life-threatening events, a CK-MM level could guide disposition.
- Bedside diaphragm ultrasound, fluoroscopy ("C-arm") and electromyography could reveal DCS and other diaphragm arrhythmias in symptomatic individuals.

Pertinent Quote:

> *"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."* **Lopes (1991)** [18]

Background:

Bearhugs hurt. They can also be lethal when unable to expand the ribcage to breathe. Such symptoms alone are concerning, but especially so when they occur spontaneously to a sleeping child.

The patient is now a practicing male, 53-year-old medical doctor of Jewish ancestry. He recounted a history of breathing emergencies that affected him sporadically throughout his childhood and youth (see ***Patient's Perspective***): Beginning at 7 or 8 years old alone in bed one night, he awakened gasping for air in a constricting, painful bearhug. There was no panic, rather he was baffled by the involuntary opening of his mouth at first. He could not breathe in at all despite attempted forced inspirations. There was no history of panic attacks or other psychiatric disorders. No sleep problems or child abuse. The cramp-like, bearhug rib pain was described as excruciating, constant in intensity and distributed in a C-shape under the nipple line, radiating bilaterally from posterior-to-anterior with sternal sparing. He had the wherewithal to troubleshoot despite a growing sense of impending doom. Astonishingly, symptoms resolved immediately after learning by experimentation to partially exhale followed immediately by three short-burst, positive-pressure inspirations with pursed lips "like pilots breathe in a centrifuge". With repeated episodes over the years, he recognized painful rib fasciculations to be prodromal and could be aborted by the rescue breaths.

He had many risk factors overlapping with those in SIDS: male sex, gastroesophageal reflux, chronic diarrhea, residing in a colder climate, low birthweight, household cigarette smoke and deep sleeping with diaphoresis, prone positioning and a tendency to pull bed linens over shoulders and head.

We originally sought to find the cause for our patient's concerning nighttime symptoms. Clinical reasoning substantially reduced the list of differential diagnoses using key historical features: recurrent, spontaneous, nocturnal, sudden on- and offset, cramp-like bilateral rib pain with simultaneous inspiratory arrest (**Table 'S'**). The diagnoses with highest likelihood were cramps of the bilateral external intercostal muscles and those of the diaphragm. Both are inspiratory muscles; however, the diaphragm is *obligatory* and solitary whereas the intercostals are *accessory* and paired into left and right groups (**Fig. 1**). Occam's razor and deductive reasoning both favoured the simplest explanation: diaphragm cramping. Thus, in generating a differential diagnosis for pediatric bearhug pain with life-threatening gasping and apnea, it

inadvertently led to a novel mechanism of acute respiratory pump failure. One that could cause sudden, unexpected deaths and is reversible given our patient survived.

Mammals have two vital pumps: the heart and diaphragm. Yet the ratio of their research papers in sudden unexpected deaths is 250-to-1, respectively, predominantly in sudden infant death syndrome (SIDS). The diaphragm has essentially been ignored despite being of equal importance. Given this unique form of respiratory arrest may not be reversed in some individuals, it is important to realize they would not have lived through it, let alone be recruited into research studies (*survivorship bias*). [1] Consequently, the full spectrum of patient presentations may be missed. Such victims would only receive their diagnosis *post-mortem:* SIDS, sudden unexplained death in childhood (SUDC) and sudden cardiac death, depending on age.

SIDS and SUDC are distinguished arbitrarily based on age (under/over 1 year, respectively). There is no evidence suggesting different causes, however, the incidence of SIDS is 38-times greater. [2] Victims are typically found prone in bed and have congested, wet lungs at autopsy with intrathoracic petechial hemorrhages suggestive of asphyxia (Tardieu spots). [3, 4, 5] They are found in over 80% of SIDS and 50% SUDC. [6, 7] Based on their intrathoracic distribution, a terminal struggle to inspire from an upper airway obstruction was suggested by *Krous* (1984), however, there has been no supporting evidence.

Diaphragm fatigue leading to failure in SIDS was proposed by *Siren & Siren* (2011). [8] In their fascinating critical diaphragmatic failure hypothesis, they posited progressive *fatigue* terminating in diaphragm *failure* typically occurs from a non-lethal childhood infection superimposed on underdeveloped respiratory muscles as well as prone positioning and rapid eye movement-sleep inactivation of respiratory accessory muscles (RAM). They later added contributions by hypomagnesemia, overheating and tobacco smoke (SIDS risk factors). However, given these conditions are not uncommon in childhood, one would expect a higher SIDS incidence. Progressive diaphragmatic fatigue implies a period of several hours of respiratory distress leading to sudden death, which is not observed in most SIDS cases (however, could be subclinical). It is also missing a 'smoking gun' mechanism that precipitates the failure itself (respiratory arrest). Regardless, the hypothesis has its merits in parallel with our case, both placing the locus at the diaphragm.

Hypothesis:

Non-cardiac, sudden unexpected death is primarily caused by *novel* "diaphragmatic cramp-like spasm" (DCS)-induced respiratory arrest.

Explanation of Hypothesis:

Cramping of a skeletal muscle renders it unable to perform work, effectively paralyzing it by contracture. In the case of the diaphragm, bilateral cramping (as described by the case patient) should then lead to a state equivalent to bilateral diaphragmatic paralysis (BDP). BDP induces diaphragm arrest/apnea when the paralysis is neurologically complete and occurs suddenly in those with weak RAM. This is the case in phrenectomized very young animals. [9] It is thought they are unable to support chest expansion by RAM contractions independent of a functioning diaphragm because of their underdeveloped, untrained state. [8] Resultant syncope, cardiac arrest and death would occur within minutes if not reversed.

Diaphragm cramping has not been described in the medical literature. Paralysis and paresis (weakness) occur by pathologies affecting the CNS, phrenic nerve(s), diaphragm, RAM or combination thereof (**Table 2**). Some are gradual in onset, unilateral and affect just the diaphragm such as phrenic nerve compression by a slow-growing tumour. When diaphragm paresis is slow-developing, compensatory RAM recruitment and training occur. Other causes can be sudden-onset, bilateral and involve both the diaphragm and RAM including spinal cord transections, electrocutions and neurotoxins like curare, succinylcholine and *nicotine* (a well-known SIDS risk factor, *vide infra*). [10, 11] Electrolyte disorders, acidosis (metabolic and respiratory) and malnutrition contribute to diaphragm fatigue and may play a role in SIDS and eating disorder deaths. [13, 14] Hypomagnesemia weakens respiratory muscles in children and is thought to increase muscle tonicity and excitability in SIDS. [15] Acidosis exacerbates this by increasing renal excretion of magnesium (and calcium). [16] Finally, hypercapnia reduces diaphragmatic contractility. [17] Along with mild hypoxia, it occurs by rebreathing exhaled gases trapped on the (horizontal) bed, worsened by loose blankets, soft toys and bed companions (all SIDS risk factors). In summary, a wide variety of insults affect the respiratory pump and can

cumulatively weaken or even suddenly paralyze it. Another important, but less known cause, is sleep itself.

Normally, RAM augment diaphragm function in times of increased demand, even during sleep. However, with the onset of REM-phase, CNS-mediated inhibition of all body skeletal muscles occurs *including the RAM*. Suddenly, an additional workload is placed on the diaphragm to maintain ventilation; a process known as *respiratory load sharing*. [18] It was *Siren & Siren* who proposed this could trigger respiratory failure in infants with diaphragm fatigue. [8, 19] We completely concur but add that diaphragm cramping, as a result of escalating muscle tonicity and hyperexcitability secondary to fatigue, is the 'smoking gun mechanism'. In other words, DCS-respiratory arrest is triggered by REM-sleep. Notably, this mirrors exercise-induced limb fasciculations and cramps that occur in fatigued muscles which are untrained and/or overworked. [20]

Fortunately, our 7-year-old patient was able to reverse the diaphragm arrest of DCS by auto-resuscitating (essentially *breathing out to breathe in*). In infants though, clearly this is not possible (**Table 2**). Upon waking from the painful cramp of DCS, the effort to expand the chest and breathe by reactivated RAM action is futile independent of a functioning diaphragm because of their underdeveloped, untrained state. In fact, their desperate, last-ditch pumping contractions to inspire would be resisted by the forces of pulmonary compliance (tissue elasticity) and the tetanically contracted, immobilized diaphragm (translation). This would act like an airway obstruction — one that disappears post-mortem — and could explain the mysterious obstruction postulated in SIDS by *Krous*. Furthermore, negative intrathoracic pressures would build with RAM contractions. The vacuum effect shunting systemic blood into the thorax, primarily the lungs and thymus, rupturing intrathoracic-lining capillaries by excessive hydrostatic pressures. This could explain the heavy, wet lungs and Tardieu petechiae found at autopsy in many sudden, unexpected deaths (**Fig. 2**). Interestingly, this unusual hemodynamic phenomenon would be exacerbated by *clamping* of the inferior vena cava and aorta at their apertures by the hypercontracted diaphragm. Lastly, this scenario is reminiscent of noncardiogenic pulmonary edema in living subjects. DCS could be responsible.

Respiratory arrest by DCS has escaped detection because of high mortality, it mimics other conditions (seizure, choking, cardiac arrest) or is unwitnessed, is silent (inspiratory arrest), nearly invisible (diaphragm and the airway obstruction are internal) and leaves few traces at autopsy

(*vide infra*). Like ventricular fibrillation, pathological pump contractions do not persist postmortem.

Evidence Supporting Hypothesis:

Using diaphragm and intercostal surface electromyography (EMG), *Lopes* (1981) found REM-sleep RAM inactivation was associated with apnea in 7 of 12 preterm infants with diaphragmatic fatigue. Some required stimulation and even short-term mechanical ventilation. [18] (Troublingly, what happens to infants experiencing identical issues *at home* is unknown.)

Studies demonstrating immediate respiratory arrest and death in experimentally phrenectomized animals, thereby inducing acute BDP, occurred predominantly in the *very young* (despite functioning RAM). [9] This was supported in children by two reports of diaphragmatic paralysis caused by phrenic nerve injuries complicating cardiac surgeries. In the first, severe respiratory distress occurred repeatedly in four infants with acute BDP despite active RAM, some requiring repeat intubations. [21] In the other, in 168 postoperative children with unilateral and bilateral DP, prolonged mechanical ventilation was needed in many. [22] *Younger*, *smaller* infants (both SIDS risk factors) and those with BDP (a "respiratory arrest risk factor") had longer postoperative stays.

In adults requiring mechanical ventilation on an intensive care unit, 53% had diaphragmatic dysfunction (DD) on admission. [23] Mortality was higher in patients with DD, either on initiation of mechanical ventilation or during the subsequent ICU stay, as compared to those who never developed DD (35 vs. 0%, $p = 0.04$).

An analysis by *Poets* (1999) of nine home-monitored SIDS victims with a median age of 4.8 months revealed bradycardia, gasping and apnea had occurred terminally. [24] This is consistent with our patient's own report. "Hypoxemic ineffective gasps" were detected (rapid inspiratory movements), followed by a cessation in breathing and no rise in heart rate. In support of *Krous'* earlier hypothesis, this suggested hypoxemia was caused by airway obstruction (not central apnea).

Although laryngospasm was proposed in causing SIDS, a reversible cause of airway obstruction, it did not cause respiratory failure or death in anesthetized dogs. [25] Interestingly

however, total cessation of diaphragmatic EMG activity occurred temporarily in one animal whereas another had *erratic diaphragm contractions*.

Histological signs consistent with DCS at SIDS autopsy: *Kariks* (1989) reported focal areas of acute, anoxic muscle fiber coagulative necrosis in 198/242 (82%) of SIDS victims' diaphragms. [26] "Contracture (contraction) bands", the presence of which indicated recent origin of irreversible cell injury, were also found (**Fig. 3**). They are produced by an extreme compaction of sarcomeres. Such findings reflected "lethal diaphragmatic damage had occurred *terminally* under hypoxic conditions and from a *hypercontractile state*". [27] Some near-miss SIDS cases demonstrated diaphragm inflammation (myositis) and fibrous scars.

Tobacco smoke exposure is a well-known SIDS risk factor, yet the mechanism remains unknown. High nicotine levels were found in the lungs of SIDS victims compared to controls. [28] Comparatively, in nicotine toxicity, death occurs by rapid respiratory paralysis from neuromuscular block "at the diaphragm". [29] *In vitro*, nicotine induced skeletal muscle fatigue as well as twitches/fasciculations and tetany/contractures (neuromuscular hyperexcitability). [30, 31] It is therefore plausible infants exposed to tobacco *smoke* — typically while sleeping *upstairs* in *heated* homes in colder climates (the latter also a SIDS risk factor) — are at risk for DCS-induced respiratory paralysis by absorbed nicotine.

Viral respiratory tract infections, bacterial toxins, dehydration, sepsis, lactic acidosis, hypercapnia and various electrolyte abnormalities also contribute to skeletal and diaphragm muscle fatigue with hyperexcitability. [32, 33, 34] Contractile dysfunction and delayed muscle relaxation are involved, raising the potential for development of muscular contractures/tetany.

Evidence Against Hypothesis:

Neonates with diaphragmatic flutter (DF) up to 300/min are still able to breathe normally. The flutter is obvious on clinical examination but in four resulted in gradual respiratory distress requiring continuous positive airway pressure in two and mechanical ventilation in one. [35, 36] Apnea was not observed. CPR was not required and the deterioration in respiratory effort was slow.

In another case series of three infants 1-20 weeks old with restricted lung function due to bronchopulmonary dysplasia and hospitalized because of respiratory syncytial virus bronchiolitis, DF of 150 to 350/min was detected by a combination of electrophysiological monitoring techniques (e.g., inductive and impedance plethysmography, electrocardiography, pulse oximetry, pneumography). [37] During brief DF periods there were no falls in oxygen saturations or heart rate and apneas were not present. The respiratory rate during DF did not differ from the rate preceding flutter. None of these infants subsequently succumbed to SIDS.

A reason why the above examples cited against our hypothesis may not be applicable to what we propose is that DF might be at the milder end of a *spectrum* of diaphragmatic hyperexcitability disorders ("diaphragm arrhythmias"), whereas the paralysis of DCS occupies the severe end (along with diaphragmatic tetany respiratory arrests from neurotoxins, electrolyte disorders and electrocutions). [38] Similar to tetany, this is where flutter is thought to merge into a high-amplitude, continuous contraction series.

Confirmation of Hypothesis:

Future *in vivo* investigations should identify DCS as a cause of respiratory distress/apnea. In infants hospitalized for acute life-threatening events, this could be accomplished by the aforementioned electrophysiological techniques along with diaphragmatic EMG, bedside ultrasound and fluoroscopy to detect abnormal contractions. Also, upon ER presentation, a total creatine kinase or CK-MM level (muscle type) could screen for muscle spasms. CK-MM is released by cramped skeletal muscles and is expected to be elevated in DCS. [39]

Experiments to reproduce DCS could be done by delivering electrical currents to intact diaphragms. Rebreathing exhaled gases (or CO_2 mixtures) in dehydrated, septic, nicotine-exposed animals with induced metabolic acidosis might also reproduce it.

Given marked diaphragmatic histological abnormalities exist in SIDS, this needs to be reevaluated. Diaphragm biomarkers could then be developed. Finally, all autopsies in sudden unexpected death need to include diaphragm histology. [40,41]

Implications of a Confirmed Hypothesis:

Our 7-year-old patient would have perished had he not autoresuscitated. His rescue breath technique should be taught to all children capable of understanding.

A DCS risk stratification tool based on SIDS risk- and preventative factors and hydration status could be developed. Those with highest scores should receive nocturnal apnea monitoring by diaphragmatic EMG.

All parents and caregivers need pediatric CPR education. In particular, to maintain a patent airway and confirm chest rise with each rescue breath. Lastly, to minimize nocturnal dehydration, there is no harm in giving plenty of fluids *prior to sleep*.

TABLES AND IMAGES

Table 1 – Etiologies of Respiratory Muscle Paralysis and Paresis. The CNS, phrenic nerve(s), diaphragm and/or RAM may be involved and can be combined. Insults can be sudden or gradual, unilateral or bilateral and complete or incomplete. Loss of neuromuscular function is *complete* in paralysis and *partial* in paresis (weakness).

		Onset	Side	RAM Involvement
Multi-organ (CNS, phrenic nerve(s), diaphragm, respiratory accessory muscles)				
Electrocution	Lightning, low- and high-voltage shocks	S	Both	✓
Neurotoxin	Nicotine, botulism, tetanus, curare, organophosphates, carbamates, tetrodotoxin, strychnine, envenomations	S	B	✓
Medication	Neuromuscular blockers, aminoglycosides	S	B	✓
Electrolyte	Hypomagnesemia, hypocalcemia, low and high potassium, hypophosphatemia	S,G	B	✓
Metabolic	Acidosis *(DKA)* , endocrinopathies (*pheochromocytoma crisis), eating disorders*	S,G	B	✓
Inflammatory	Vasculitis, pneumonia, pleurisy, herpes zoster, SARS-CoV-2 (COVID-19)	G	B	✓
Neuropathic & myopathic	Guillain-Barré syndrome, polio, ALS, myasthenia gravis, Lyme disease, rabies, muscular dystrophy, polymyositis, dermatomyositis, inclusion body myositis	G	B	✓
Phrenic Nerve				
Traumatic	Cervical spinal cord transection (above C5)	S	B	✓
	Cervical soft tissue injuries (blunt, penetrating, traction, compression)	S	U	0
Iatrogenic	Birth trauma (asphyxia), chiropractic manipulations	S	Both	0
	Cardiothoracic surgeries, cardiac cryoablation	S	Both	0
Compression	Cervical osteoarthritis, tumours (bronchogenic, mediastinal), aortic aneurysm	G	U	0
Diaphragm				
Traumatic	High-velocity: contusion, hemorrhage, rupture	S	Both	0
	Low-velocity: *winding injury* (celiac or solar plexus syndrome)	S	Both	0
Exposures	*Cold water submersion, conducted electrical devices (Taser, stun gun)*	S	B	0
Spontaneous	*Diaphragmatic cramp-like spasm*	S	B	0

RAM: respiratory accessory muscle, 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 2 – Hypothetical Sequence of Respiratory Arrest by Putative Diaphragmatic Cramp-like Spasm (DCS). This is a hypothetical example of an otherwise healthy 3-month-old infant with a runny nose, nasal congestion, mild cough and loose stools over past 24 hours. He is sleeping alone in a crib in a smoking, heated household in winter. Heart rate, oxygen saturation and breathing movements (but not respirations) are wirelessly monitored by parents using a typical home SIDS device.

1	Progressive DD (fatigue) develops secondary to viral respiratory infection, prone sleeping (in an *upstairs* bedroom of a *heated* household) and nicotine exposure/absorption from *cigarette smoke*.
2	Fluid losses from fever and bicarbonate-rich diarrhea over past 24 hours. Along with overheating and rebreathing of exhaled gases from loose, heavy bed blankets, mild hyperthermia, mild hypoxia, moderate hypercapnia and mild-to-moderate metabolic and respiratory acidosis develop. All worsen DD.
3	Similar to fatigued limb muscles, diaphragm muscle tone and neuromuscular excitability increase.
4	Physiologic RAM recruitment compensates for the DD. Inspiratory intercostal muscles activated. Observed bedside as rib retractions.
5	Falls asleep. Physiologic REM-sleep inactivation of RAM by CNS. Excess workload suddenly placed on fatigued diaphragm, pushing it past cramp threshold. Precipitates the painful, contracture-like diaphragmatic cramp of DCS that paralyzes the diaphragm and induces immediate inspiratory arrest (apnea).
6	Oxygen saturations begin to slowly drop yet insufficient to trigger alarm.
7	Infant wakes from the painful cramp (sensed as a bearhug). Unable to breathe/cry out because of inability to inspire ("ineffective gasping"). RAM become reactivated.
8	RAM contract furiously independent of a functioning diaphragm to expand ribcage to breathe. Met with combined resistance of pulmonary compliance and the hypercontracted, immobilized diaphragm. Like breathing against a 100% upper airway obstruction, RAM contractions build negative intrathoracic pressures (yet insufficient to expand lungs).
9	No alarm because chest movements continue with each inspiratory effort.
10	Vacuum effect shunts systemic blood into intrathoracic organs, primarily the lungs. Capillaries rupture from high hydrostatic pressures, forming petechial hemorrhages on the linings of intrathoracic organs. Exacerbated by effective clamping of inferior vena cava by the hypercontracted diaphragm (aorta too possibly).
11	Infant loses consciousness as RAM weaken from hypoxia.
12	Hypoxia, bradycardia and/or lack of body movements finally trigger the alarm, but only 3-5 minutes remain before cardiac arrest.
13	Cyanotic, unresponsive child found by panicked parents who call 911 and initiate CPR. Chest compressions started. Rescue breaths attempted but met with airway resistance from improper neck positioning and the hypercontracted, immobilized diaphragm. Parents not educated to open airway or look for chest rise.
14	Chest compressions resumed but the primary respiratory issue remains unaddressed.
15	Rescue breaths done hurriedly and again without confirmation. Panic and ineffective care continue.
16	Cardiac arrest.

DCS: diaphragmatic cramp-like spasm, DD: diaphragm dysfunction, RAM: respiratory accessory muscles, REM: rapid-eye-movement sleep

Figure 1 – Muscles of Respiration. The primary inspiratory muscles are the diaphragm and paired left and right external intercostal muscles (ICMs, lavender). The latter reduce diaphragmatic workload in adults by their bucket handle movements which widen the ribcage. Theoretically, if the ICMs were to suddenly fail, apnea would not occur as long as the diaphragm continued functioning. Contrarily however, if the diaphragm suddenly and completely failed, apnea and respiratory arrest could.

With permission by www.concept2.co.uk/training/breathing.php.

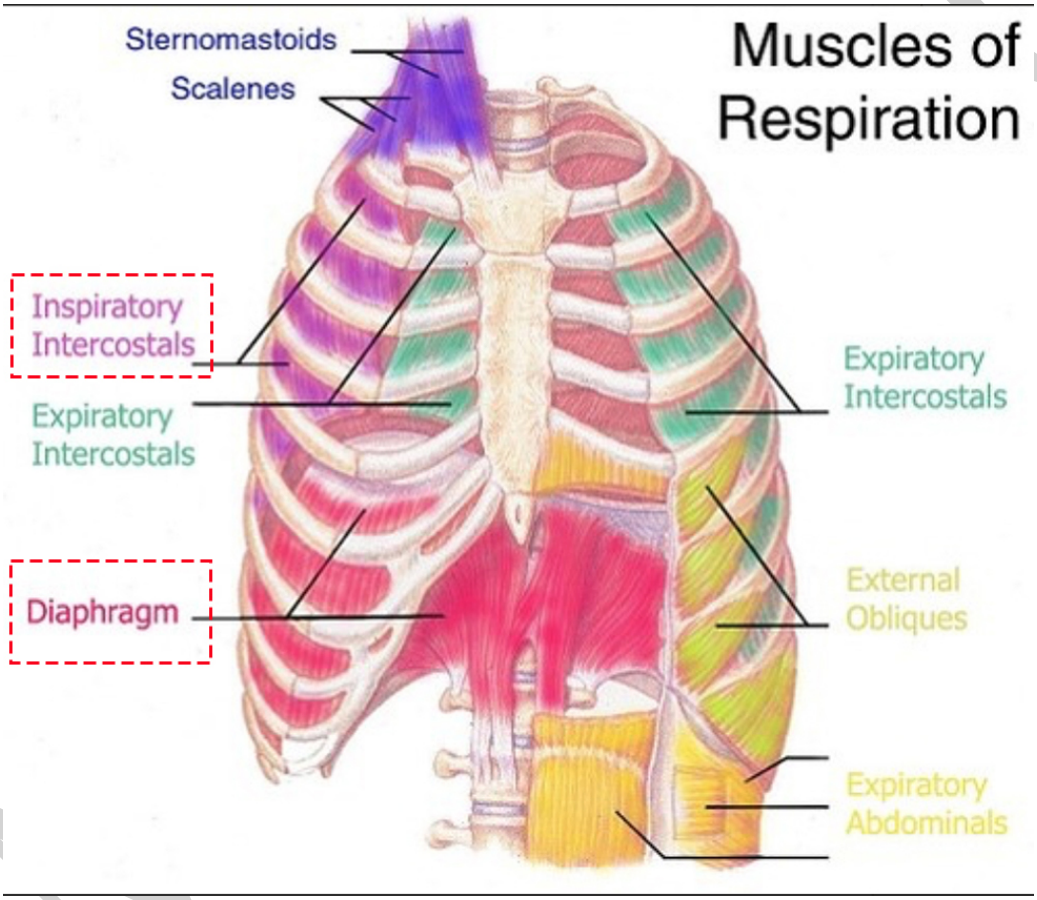
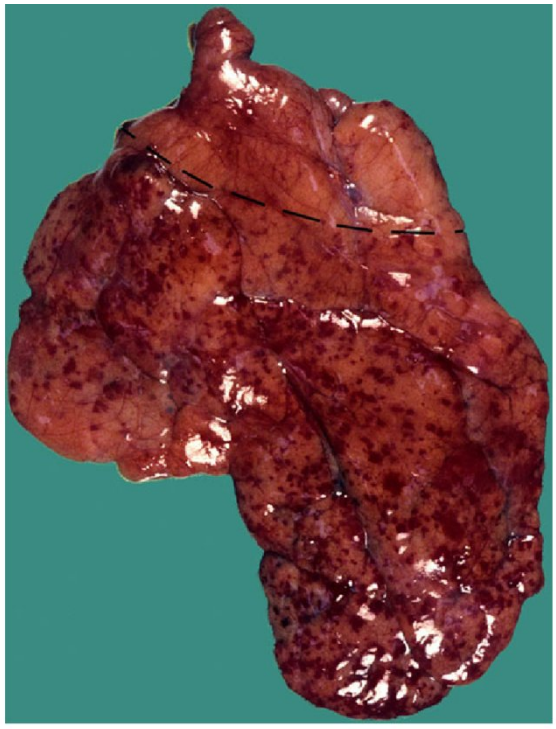


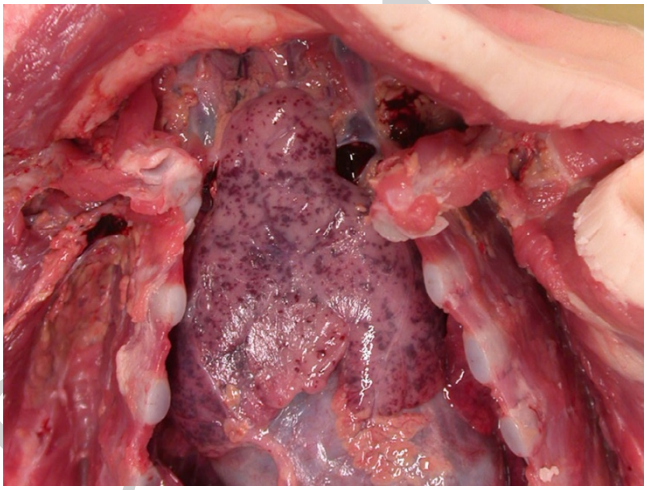
Figure 2 – Thymus Gland in Asphyxia. A) Beckwith's sign. The inferior, larger portion of the thymus is anatomically situated within the thoracic cavity whereas the smaller, superior segment is not (interrupted line). Sharp increase in the number of Tardieu petechial hemorrhages in the intrathoracic segment. **B)** Neonatal thymus (atop the heart) with Tardieu petechiae.

A)



Courtesy of Prof. Roger W. Byard.
In "Sudden Death in the Young", 3rd Ed.
Cambridge Univ. Press 2010.

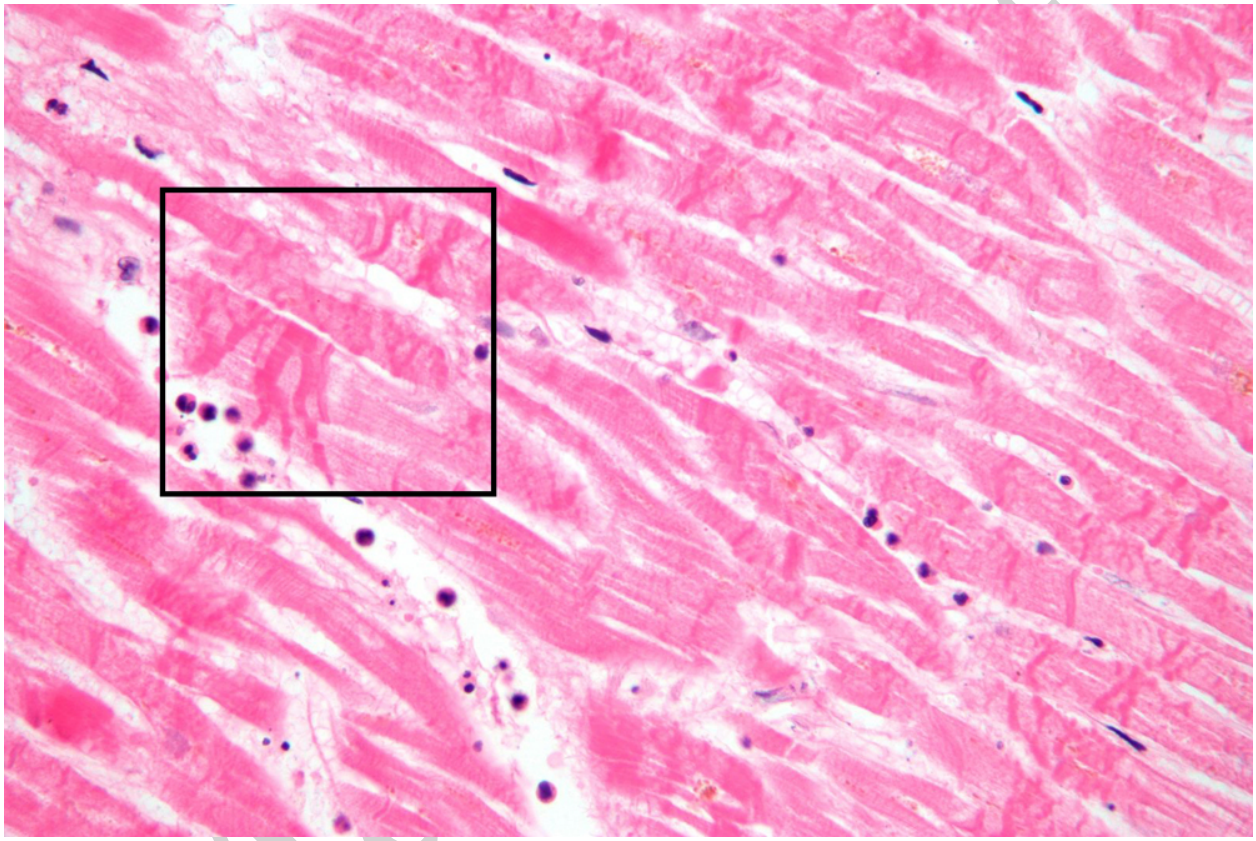
B)



Courtesy of Prof. Paul Goldwater.
In "Increased thymus weight in SIDS compared to controls: The role of sub-clinical infections." Am J Hum Biol. 2021.

Figure 3 – Contraction Band Necrosis. High magnification micrograph of cardiac myocytes oriented longitudinally. Contraction band necrosis appears as intensely eosinophilic (dark pink) thick bands spanning the width of the sarcoplasm (box outline). Indicative of acute anoxic sarcomere hypercontraction and rupture. A similar process occurs in the majority of diaphragms in SIDS victims.

Courtesy of 'Nephron', CC BY-SA 3.0. Wikimedia Commons, 2009.



SUPPLEMENTARY MATERIALS

1. Patient's Perspective

This account is written by a practicing medical doctor of Jewish ancestry born in 1970 (53 years old). After receiving trauma counselling in late 2022 he recalled in great detail life-threatening breathing emergencies that had awakened him from sleep sporadically 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 survival (defense) mechanism. Notably, he had multiple childhood risk factors overlapping with those identified in SIDS.

"One night while alone in bed at 7 or 8 years old, I suddenly awoke from an excruciating, cramp-like pain in my ribs that felt like someone had picked me up from behind in a tight bearhug. The pain radiated from back-to-front in a C-shaped distribution with sternal sparing. I couldn't breathe in at all and was also baffled because my mouth had opened involuntarily at first as I gasped for air. 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 nobody was behind me. The bearhug and inability to inhale (apnea) persisted.

Despite the growing sense of impending doom, I began to troubleshoot by experimentation. When I tried inhaling more forcefully though it was met with equal and opposite, complete resistance to airflow. It was futile. My next test, to exhale, was successful and I remember telling myself not to lose all the air in my lungs so to conserve it. I still couldn't breathe, and the pain continued. I did not have stridor, choking, fullness or a foreign body sensation in my throat and no palpitations or chest discomfort.

What I did next was lifesaving.

I tried something new by partially exhaling followed immediately by three short-burst inhalations with pursed lips (to increase inspiratory pressure). To my relief, the pain and apnea resolved completely. Crisis averted, so I went back to sleep *as only a seven-year-old can despite a near-death experience*. Soon afterwards I noticed how a pilot on TV, while spinning in a centrifuge, used the same distinctive pursed-lip breathing technique. I had never seen that before.

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

The breathing emergencies recurred sporadically throughout my childhood and youth but only at night while fast asleep. I do not know if I had any associated illnesses, however, it's interesting I had mild diarrhea with most bowel movements (which also continued throughout my childhood and youth undiagnosed).

Eventually I recognized, in my sleep, prodromal flickering pains (fasciculations) in my ribs to be a warning sign of the impending bearhug pain and inspiratory arrest like that of the first episode. I would wake from this and use my rescue breaths (RBs) to abort the full-fledged attack. I can say with certainty the fasciculations and pain felt like that of a limb muscle cramp. I should also note the full bearhug pain came on *just at the very end of expiration* (and could be aborted by quickly breathing in). I can still recall how it always spread in a millisecond from a spot in my right posterolateral ribs to the encircling, painful bearhug.

The RBs were so loud and high-pitched, I remember awakening one night to their sound. It appears I had grown so accustomed, *I did them in my sleep*. Oddly, I also recall telling myself that night 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 house, therefore, between ages 17 and 23. I'm not certain if I had any further 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 confirmed and definitively treated a congenital hiatal hernia. I recovered well, quickly gained weight and do not recall having reflux symptoms as I grew older.

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

In addition, beginning at roughly 10 years old, I occasionally become suddenly and extremely fatigued during prolonged, intense exercise. I learned it occurred when not eating properly beforehand. Carbohydrate-rich foods prevent and abort symptoms. Condition undiagnosed at the time of writing but consistent with McArdle's (glycogen storage) disease.

Social history: I am the second male child of a Gravida 4, Para 2 smoker. Brother denies sleep-related pain or breathing issues. I slept alone in an *upstairs* bedroom in a household containing *cigarette smoke* that was *heated* in wintertime (smoke rises).

Notably, I had stopped thumb-sucking around the same age as the onset of the breathing emergencies (important because pacifiers are known to be SIDS protective). I cannot think of anything else that might have changed (that could explain why this all started in my childhood as opposed to infancy).

In terms of childhood risk factors overlapping with SIDS, mine were numerous including male sex, low birthweight, 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 history of seizure, 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 muscle coordination possessed by an older child. It is only now upon reflection as an adult do I realize how lucky I am to be alive.

I am determined to eradicate DCS.

Sleeping children need our help…<u>now</u>."

2. *Supplementary Table "S"*

Table "S" – Differential Diagnosis of Case Patient'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 case patient's history were recurrent, nocturnal, spontaneous sudden on- and offset, cramp-like bilateral rib (bearhug) pain with simultaneous inspiratory arrest (apnea). Clinical reasoning yielded five final diagnoses with relative degrees of clinical confidence.

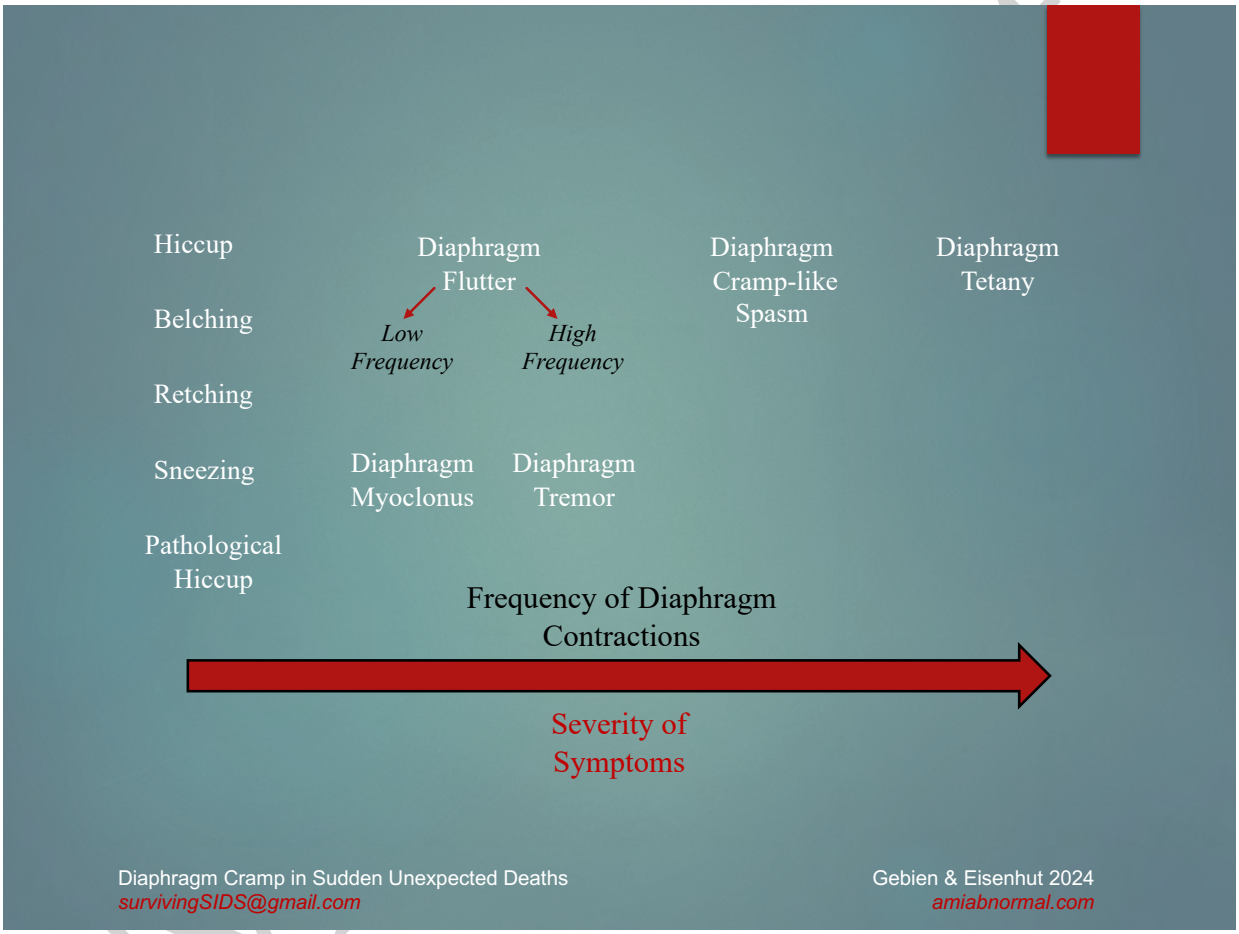
A. Unilateral and Bilateral Pediatric Rib Pain*		**Apnea?**	**Recurrent?‡**
	Rib fracture, muscle strain, intercostal neuralgia	No	Possible
	Fibromyalgia, juvenile rheumatoid arthritis	No	Possible
	Pleurisy, pleurodynia	No	Possible
	Tumours of chest wall and ribs	No	Unlikely
	Pneumothorax, pneumomediastinum	No	Unlikely
	Electrical injury	**Possible**	**Possible**
	Panic attack, somatoform and fictitious disorders, malingering	**Possible**	**Possible**
	Child abuse	**Possible**	**Possible**
	Intercostal muscle cramp/spasm	**Possible**	**Possible**
	Diaphragmatic cramp-like spasm	**Possible**	**Possible**
B. Nocturnal 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/spasm	**Yes**	**Possible**
	Diaphragmatic cramp-like spasm	**Yes**	**Possible**
Nervous System	Seizure	No	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 (solar or celiac plexus syndrome)	**Possible**	Unlikely
C. Recurrent bilateral rib (bearhug) pain and apnea*‡		**Clinical Confidence**	
	Repeated electrical injuries	Low	
	Panic attack, somatoform and fictitious disorders, malingering	Medium	
	Child abuse	Medium	
	Bilateral intercostal muscle cramps	**High**	
	Bilateral diaphragmatic cramp-like spasm	**High**	

* List is inexhaustive. ‡ "Recurrent" refers to relapsing and remitting.

Bold: higher clinical suspicion, *Italics* : putative (unproven)

3. Supplementary Table "T"

Table "T" – Spectrum of Diaphragm Hyperexcitability Disorders. As the frequency of diaphragm contractions increases, symptoms worsen, and respiratory distress prevails. These could alternatively be termed, "diaphragmatic arrhythmias".



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