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

Dov Jordan Gebien MD (*ABEM*), MSc (*Pathol.)*

Michael Eisenhut MD FRCPCH FRCP DTM&H

March 20, 2024

Short Title: Diaphragm Cramp in Sudden Deaths

Affiliations: Michael Eisenhut: Luton & Dunstable University Hospital, Lewsey Road, Luton, LU40DZ, United Kingdom

Address correspondence to: Dov Gebien, Toronto, ON. Canada. survivingsids@gmail.com

ORCID ID (Gebien): 0000-0002-3384-5865

ORCID ID (Eisenhut): 0000-0002-9944-9320

Preprint DOI: 10.13140/RG.2.2.18091.62243

Abstract 250

Rationale: The diaphragm, a vital skeletal muscle pump, is grossly understudied.

Objective: Determine if near-miss SIDS equivalent occurred in child with paroxysmal, nocturnal "bearhug pain" and apnea.

Methods: Clinical reasoning reduced the differential to a novel diagnosis: "diaphragmatic cramp-like contracture" (DCC). Hypothesized, "non-cardiac, sudden unexpected deaths are primarily caused by respiratory arrest from DCC-induced, bilateral diaphragm paralysis" (DP).

Main Results: Literature review revealed numerous informative findings, some novel: 1) DP from all causes, in all ages induces respiratory arrest when sudden, neurologically complete, bilateral and involves respiratory accessory muscle (RAM) paralysis/weakness. Death occurred in very young, but not older infant animals with induced bilateral DP because immature RAM could not independently expand lungs, 2) RAM inactivation in REM-sleep suddenly adds diaphragmatic workload. In infants with diaphragm fatigue, this precipitated diaphragmatic failure/apnea, 3) Skeletal muscles become excitable (fasciculations, cramps) under higher workloads when fatigued. Many SIDS risk factors fatigue the diaphragm, including prone positioning, viral infections and nicotine, 4) "Diaphragmatic hyperexcitable disorders" exist on a frequency spectrum of worsening symptoms, including myoclonus and diaphragm flutter. Flutter caused disabling dyspnea (adults) and respiratory distress (neonates) requiring ventilatory support, 5) Diaphragm *contraction band* necrosis (CBN), indicative of hypercontraction injury, occurred terminally in many SIDS cases.

Conclusion: With REM-sleep onset in individuals with respiratory fatigue worsened by prone positioning, infections, nicotine and other SIDS/diaphragmatic fatigue risk factors, DCC could represent an unstable hyperexcitable disorder catalyzing diaphragm arrest-sudden death. Postmortem evidence of DCC is supported by CBN. Autopsies in sudden deaths should include diaphragm histology.

Keywords: diaphragm cramp, diaphragm paralysis, respiratory arrest, SIDS, sudden death

Abbreviations: BDP: bilateral diaphragmatic paralysis, **CK-MM**: creatine kinase-muscle type isoenzyme, **DCC**: diaphragmatic cramp-like contracture, **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

Optional 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 et al (1991)**[21]

Introduction 2487

Bearhugs hurt. They can also be lethal when unable to expand the ribcage to breathe. Such symptoms are extremely concerning, let alone when they recur spontaneously in a sleeping child.

The patient is now a practicing male, 53-year-old physician. He recounted nocturnal breathing emergencies affecting him sporadically throughout his childhood and youth: Beginning at 7 or 8 years old alone in bed one night, he awakened gasping for air in a painful, constricting bearhug. There was no initial panic, rather he was baffled by the involuntary opening of his mouth. He could not breathe despite attempting forced inspirations. There was no history of panic attacks or other psychiatric disorders, no sleep problems or child abuse. The cramp-like pain was described as excruciating, constant-intensity and distributed in a C-shape under the nipple line, radiating bilaterally from posterior-to-anterior. He had the wherewithal to troubleshoot despite the impending sense of doom. Astonishingly, symptoms resolved immediately after learning by experimentation to exhale followed 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 were prodromal and could be aborted by rescue breaths.

He had many risk factors overlapping with those in SIDS: male sex, gastroesophageal reflux, chronic diarrhea, 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 diagnose our patient's concerning symptoms. Clinical reasoning substantially reduced the differential diagnoses using key historical features: recurrent, spontaneous, nocturnal, sudden-onset, cramp-like, bilateral rib pain with simultaneous *inspiratory arrest* (still able to exhale residual air). 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 intercostals are *accessory* and paired into left and right groups of small muscles (**Fig. 1**). Deductive reasoning favoured diaphragm cramping. Thus, in generating a differential diagnosis for recurrent 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.

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 equal importance to the heart. 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 diaphragm dysfunction presentations may be missed in the literature. Moreover, such victims would only receive their diagnosis *post-mortem:* SIDS, sudden unexplained death in childhood (SUDC) or possibly 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 separate causes, however, 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] These are found in over 80% of SIDS and 50% SUDC.[6] Based on their intrathoracic distribution, a *terminal* struggle to inspire by airway *obstruction* was suggested by *Krous* (1984). However, it has not been supported.[7]

Progressive diaphragm fatigue terminating in respiratory failure in SIDS was proposed by *Siren & Siren* (2011).[8] They speculated several fatiguing factors can increase the risk of

diaphragm failure, such as non-lethal childhood infections, prone positioning as well as underdeveloped respiratory accessory muscles (RAM) and their inactivation in REM-sleep. Later, they added contributions by hypomagnesemia, overheating and tobacco smoke. Importantly, all were SIDS risk factors.[9]

Like limb muscles, the diaphragm is a skeletal muscle vulnerable to fatigue (diaphragm dysfunction) by factors that reduce contractility or increase workload. Dehydration, electrolyte disorders, hypoxia, hypercapnia, nicotine and acidosis (both lactic and respiratory) all reduce contractility (**Table 1**). Viral respiratory tract infections, bacterial toxins and sepsis also contribute.[10,11,12] Again, many of these, if not all, are SIDS risk factors.[3] In addition, fatigued skeletal muscles including the diaphragm exhibit increased tone and neuromuscular excitability (*hyperexcitability*) when the contraction relaxation phase becomes delayed. This occurs with some of the same factors listed above. *In vitro,* twitches, contractures and tetany can be induced, whereas *in vivo*, fatigued, overworked or untrained skeletal muscles exhibit fasciculations, spasms and cramps with suddenly increased loads.

Heterogenous clinical descriptors of a variety of hereby designated "diaphragm hyperexcitability disorders" exist in the medical literature. From simple hiccups, belching and retching to pathological hiccups, myoclonus, tremor and diaphragm flutter (DF), a polyonymous entity, abnormal diaphragm contractions and rhythms exist on a *frequency spectrum*. It is correlated to worsening symptoms and prognosis (**Fig. 2**).[13] Mortality might also correlate; however, survivorship bias makes this impossible to discern. Among higher frequency conditions like DF, respiratory distress becomes predominant both in children and adults. Like the heart, such disorders could alternatively be described, "*unstable* diaphragmatic arrhythmias".

Hypothesis:

Non-cardiac, sudden unexpected deaths are primarily caused by respiratory arrest from "diaphragmatic cramp-like contracture" (DCC)-induced, bilateral diaphragm paralysis.

Discussion

Diaphragmatic cramp has not been described in the medical literature to our knowledge. Cramping of a skeletal muscle renders it unable to perform work, effectively paralyzing it by contracture. Bilateral cramping of the diaphragm should therefore lead to a state equivalent to bilateral diaphragmatic paralysis (BDP). Literature review revealed a novel finding in this regard: BDP induces immediate diaphragm arrest/apnea from all causes and in all ages when the paralysis is neurologically complete and occurs suddenly in those with paralyzed or weak inspiratory RAM. Once respiratory arrest occurs, hypoxic syncope, cardiac arrest and death ensue in minutes if not reversed.

Inspiratory muscle paralysis and paresis occur by pathologies affecting the CNS, phrenic nerve(s), diaphragm, RAM or combination thereof (**Table 2)**. Some are gradual, unilateral and affect just the diaphragm, such as phrenic nerve compression by a slow-growing tumour. In this case, time allows compensatory RAM recruitment and training to occur. Other insults can be sudden, bilateral and involve both diaphragm and RAM, including cervical cord transections, some electrocutions, neurotoxins like curare and nicotine and neuromuscular blockers like succinylcholine.[14,15] Electrolyte disorders, acidosis and malnutrition likely play a role in SIDS and eating disorder deaths.[16,17] Hypomagnesemia weakens respiratory muscles in children and is thought to increase muscle tonicity and excitability in SIDS.[18] Acidosis exacerbates this by

increasing renal excretion of magnesium (and calcium).[19] Finally, hypoxia and hypercapnia also reduce diaphragm contractility.[20] They occur by rebreathing exhaled gases trapped on a bed and worsened by soft bedding, toys and bed companions (SIDS risk factors). Both would develop positive feedback cycles because a weakened diaphragm impairs alveolar ventilation. In summary, a wide variety of insults can affect the respiratory muscles and cumulatively weaken, or even paralyze them. Another important, but less known cause, is sleep itself.

Normally, RAM augment diaphragmatic function under increased demand, even during sleep. However, with REM-sleep onset, CNS inhibition of skeletal muscles inactivates them, including the RAM (but not diaphragm). Suddenly, an additional workload is placed on the diaphragm to maintain ventilation because of "respiratory load sharing".[21] It was *Siren & Siren* who proposed this triggers respiratory pump failure in infants with diaphragm fatigue.[8] We concur but add that diaphragm cramping, consequent to escalating muscle tonicity and excitability in fatigue is the "smoking gun mechanism". In other words, pump failure by DCC-respiratory arrest is triggered by REM-sleep. Notably, this mirrors exercise-induced skeletal muscle fasciculations and cramps in fatigued, untrained/overworked limb muscles.[22]

Fortunately, our patient was able to reverse his diaphragm arrest by auto-resuscitating (essentially, *breathing out to breathe in*). In infants though, this counterintuitive task is clearly not possible (**Table 3**). Instead, upon waking from the bearhug pain of DCC, efforts to expand the chest and breathe by reactivated RAM pumping action would be futile devoid of a functioning diaphragm. In fact, these last-ditch effort contractions to inspire would be counteracted by the resistive forces of pulmonary compliance (overcoming tissue elasticity) and the tetanically contracted, immobilized diaphragm of DCC (translational resistance to moving caudally). This explains why our patient could not inspire initially. It creates a novel form of

airway obstruction; an internal mechanical asphyxia that disappears post-mortem. It also supports *Krous'* hypothesis. Furthermore, negative intrathoracic pressures would build with continued RAM contractions: the vacuum effect shunting systemic blood into the thorax, primarily the pulmonary circulation, rupturing intrathoracic organ-lining capillaries by excessive hydrostatic pressures (**Fig. 3**). This could explain the heavy, wet lungs and Tardieu petechiae found at autopsy. Interestingly, this unusual pulmonary-hemodynamic phenomenon might be exacerbated by *clamping* of the inferior vena cava and aorta by the hypercontracted diaphragm at their apertures. Finally, this is reminiscent of noncardiogenic pulmonary edema in living subjects (shared pathological findings). It too involves rapid respiratory distress with increased pulmonary capillary permeabilities. Temporary, survivable obstruction by DCC or unstable DF could be responsible.

Respiratory arrest by DCC has escaped detection because it likely has very high mortality and is unwitnessed in many cases or mimics other conditions (seizure, choking, cardiac arrest). It is silent (inspiratory arrest), invisible (the diaphragm and obstruction are internal) and leaves few traces at autopsy (*vide infra*). Like ventricular fibrillation, pathological pump contractions do not persist post-mortem.

Evidence Supporting Hypothesis:

Using electromyography (EMG), *Lopes et al* (1981) found REM-sleep RAM inactivation was associated with diaphragmatic apnea in 7 of 12 preterm infants with diaphragmatic fatigue. They failed to rouse and reactivate RAM, requiring stimulation and short-term mechanical ventilation in some.[21] [Notably, infants experiencing identical issues *at home* and who died would be diagnosed with SIDS.]

In neonatal but not older infant animals with induced BDP (by bilateral phrenectomies), respiratory arrest and death occurred immediately.[23] Unlike the older ones, neonates could not support chest expansion by RAM because of an underdeveloped, untrained state. Importantly, most SIDS deaths occur in young infants 1-4 months of age. Further support comes from two reports of sudden diaphragmatic paralysis (DP) from phrenic nerve injuries complicating pediatric cardiac surgeries. In the first, severe respiratory distress occurred repeatedly in four infants with acute BDP despite active RAM, some requiring repeat intubations.[24] The other, in 168 postoperative children with unilateral and bilateral DP, prolonged mechanical ventilation was needed in many.[25] *Younger*, *smaller* infants (both SIDS risk factors) and those with BDP had longer postoperative stays.

In adults requiring mechanical ventilation in an ICU, 53% had diaphragmatic dysfunction (DD, or fatigue) on admission.[26] Mortality was higher in patients with DD, either on initiation of mechanical ventilation or during the subsequent ICU stay, compared to those who never developed DD (35 vs. 0%, $p = 0.04$).

Poets et al (1999) analyzed nine home-monitored SIDS victims with a median age of 4.8 months. They revealed bradycardia, gasping and apnea had occurred terminally.[27] (Symptoms identical to our patient's report.) "Hypoxemic ineffective gasps" were detected, followed by a cessation in breathing movements and no rise in heart rate. In support of *Krous'* hypothesis, this suggested hypoxemia was from airway obstruction.

Although laryngospasm was proposed in SIDS by causing airway obstruction, it did not induce respiratory failure or death in dogs.[28] Interestingly however, total cessation of diaphragmatic EMG activity occurred temporarily in one animal whereas another had *erratic diaphragm contractions*.

Histological signs consistent with DCC at autopsy: *Kariks* (1989) reported focal areas of acute, anoxic diaphragm muscle fibre coagulative necrosis in 198/242 (82%) of SIDS victims.[29] "Contracture (contraction) bands", the presence of which indicate *terminal* irreversible cell injury, were also found (**Fig. 4**). They are produced by extreme compaction of sarcomeres and reflected "lethal diaphragmatic damage occurred…from a *hypercontractile state*".[30] Some near-miss SIDS cases had fibrous scars. Interestingly, these histological findings are consistent with calf muscle myopathic changes in children with "incapacitating" myalgia associated with upper respiratory, influenza B infections.[31] Diaphragm samples were not taken.

In nicotine toxicity, death occurs by rapid respiratory paralysis from neuromuscular block at the diaphragm.[32] *In vitro*, nicotine induces skeletal muscle fatigue, twitches and "tetanic contractures" (hyperexcitability).[33, 34] Importantly, tobacco smoke exposure is a known SIDS risk factor. High nicotine levels were found in the lungs of SIDS victims.[35] Therefore, it is plausible infants exposed to tobacco *smoke* — notably sleeping *upstairs* in a *heated* home in colder climates (also a SIDS risk factor) — are at risk for DCC-respiratory paralysis by absorbed nicotine.

Evidence Against Hypothesis:

Neonates with DF up to 300/min were still able to breathe normally. The flutter was obvious on examination but in four, resulted in gradual respiratory distress requiring continuous positive airway pressure in two and mechanical ventilation in two.[36,37] Apnea was not observed. CPR was not required, and the deterioration was slow.

In 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 electrophysiological monitoring techniques (inductive and impedance plethysmography, electrocardiography, pulse oximetry, pneumography).[38] During brief DF periods there were no drops in oxygen saturations or heart rate and apneas were not present. Respiratory rates during DF did not differ from rates preceding flutter. None subsequently succumbed to SIDS.

A reason why the above examples cited against our hypothesis may not be applicable to what we propose is DF might be a milder form on the hyperexcitability spectrum, whereas DCC is severe (along with diaphragmatic tetany-respiratory arrests from neurotoxins, electrolyte disorders and electrocutions). Similar to tetany, this is where flutter is thought to merge into a high-amplitude, continuous contraction series.

Confirmation of Hypothesis:

In vivo investigations could identify DF and DCC as causes of respiratory distress and arrest/apnea, respectively. 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 hyperexcitability. Also, upon 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 DCC.[39]

Experiments to reproduce DCC could start by delivering electrical currents to intact diaphragms and observing for persistent contractions. Rebreathing exhaled gases (or CO_2 mixtures) in dehydrated, septic, nicotine-exposed, prone-positioned, anesthetized animals with induced metabolic acidosis could also reproduce it.

Marked diaphragmatic histological abnormalities exist in SIDS. This needs to be confirmed and reevaluated. Diaphragm biomarkers could then be developed. Finally, autopsies in all sudden, unexpected deaths should include diaphragm histology.[40]

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 DCC 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, possibly by diaphragmatic EMG.

All parents need pediatric CPR education, in particular to maintain a patent airway and confirm chest rise with rescue breaths. Lastly, there is no harm in giving oral fluids *at bedtime* (minimizing dehydration) and ventilating the bedroom with a fan (reduce rebreathing).

Acknowledgements: Dr. John W. Crosby MD (Toronto, ON), Dr. Paul Goldwater FRACP, FRCPA (Adelaide, Australia), Mr. Pontus Siren (Switzerland), Mr. Glenn Morley (Toronto, ON), Ms. Barb Rovet (Toronto, ON), Dr. Deepa Takhar MD (Toronto, ON), Mr. Sergey Frey (Toronto, ON).

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TABLES AND IMAGES

Table 1 – Diaphragm Workload and Fatigue/Excitability Factors. The diaphragm is prone to fatigue and work overload by a variety of factors. Many are SIDS risk factors. Prematurity predisposes to incomplete development of respiratory muscles. There are also less fatigue-resistant diaphragm muscle fibres in younger, smaller, incompletely developed infants. **A)** The male diaphragm works harder and fatigues faster than females. Prone positioning forces the diaphragm to work harder compared to supine. REM-sleep places a sudden workload on the diaphragm. **B)** Nicotine induces skeletal muscle fatigue and excitability in vitro. Similarly, fever, acidosis, dehydration and electrolyte disorders lower the cramp threshold of skeletal muscles leading to fatigue and hyperexcitability. Influenza B predisposes to myopathy in children. Bacterial toxins in sepsis impair diaphragm contractility, increase relaxation time (rats) and caused death by respiratory arrest (dogs). Hypercapnia and respiratory acidosis from CO_2 rebreathing both reduce muscle contractility. Both hypercapnia and hypoxemia create positive feedback cycles by reducing alveolar ventilation secondary to diaphragm fatigue.

A) Increased diaphragm workload	**B) Diaphragm Fatiguing and Excitability Factors**
Prematurity/low birth weight (underdeveloped RAM)	Prematurity/low birth weight (diaphragm fibre composition)
Male gender	Household tobacco smoke (nicotine)
Prone resting position	Overheating & diaphoresis (loss of body fluids, NaCl, K, Ca, Mg, Phos)
REM-sleep	Childhood infections (gastroenteritis, URI)
	Fever and fluid loss
Bronchopulmonary dysplasia?	Electrolyte disorders (NaCl, K, Ca, Mg, Phos)
Pacifier weaning?	Viremia, bacterial toxins
	Sepsis
	Lactic acidosis (hypovolemic shock, stool bicarbonate loss)
	Rebreathing exhaled gases
	Hypoxemia
	Hypercapnia
	Respiratory acidosis

RAM: respiratory accessory muscles, Phos: phosphate, URI: upper respiratory infection

Table 2 – 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 contracture*	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 3 – Hypothetical Sequence of Respiratory Arrest by Putative Diaphragmatic Cramp-like Contracture (DCC). This is a hypothetical example of an otherwise healthy 3-month-old infant with a runny nose and congestion, 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 being wirelessly monitored by parents using a typical home SIDS device.

1	Progressive DD (fatigue) develops secondary to viral respiratory infection, prone sleeping and nicotine exposure/absorption from *cigarette smoke* (in an *upstairs* bedroom of a *heated* household).
2	Fluid losses from fever, sweating and bicarbonate-rich diarrhea over past 24 hours. Along with overheating and rebreathing of exhaled gases from loose and heavy bed blankets, dehydration, 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 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 bearhug of DCS that paralyzes the diaphragm and immediately induces inspiratory arrest (apnea).
6	Oxygen saturations begin to slowly drop yet insufficient to trigger alarm.
7	Infant wakes from the cramp/apnea. Unable to cry out because of inability to inspire ("ineffective gasping"). RAM become reactivated by CNS.
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	Internal 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. Potentially exacerbated by effective clamping of inferior vena cava by hypercontracted diaphragm.
11	Infant loses consciousness as RAMs 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.

CNS: central nervous system, DCC: diaphragmatic cramp-like contracture, 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.*

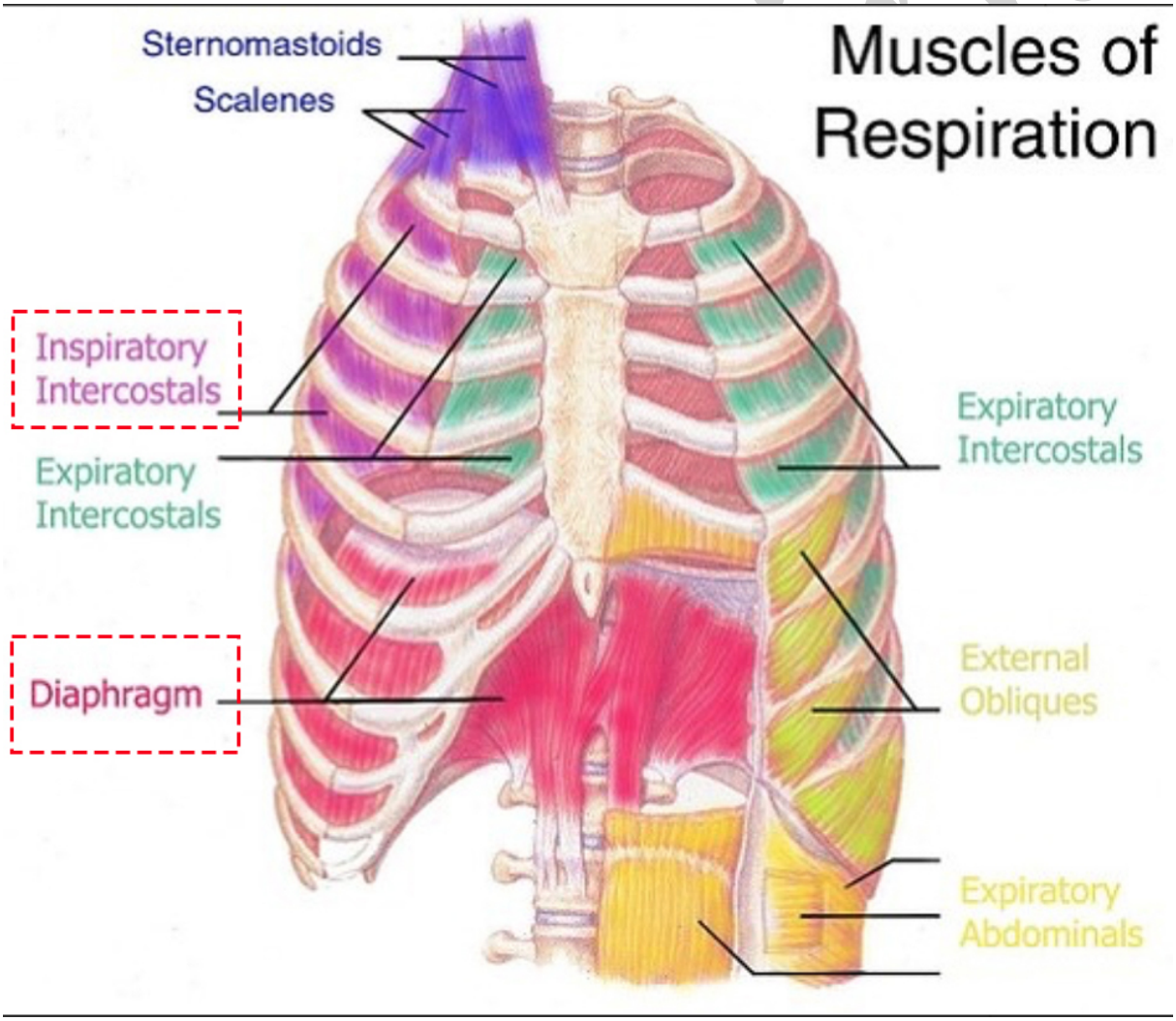


Figure 2 – Spectrum of Diaphragm Hyperexcitability Disorders. As the frequency of supranormal diaphragm contractions increases, symptoms worsen, and respiratory distress predominates. "Respiratory" myoclonus and tremor refer to contractions of both diaphragm and accessory muscles. Flutter can be mildly symptomatic or severe whereas diaphragm cramp-like contracture and tetany exhibit respiratory arrest. They could alternatively be described as, "*unstable* diaphragm arrhythmias".

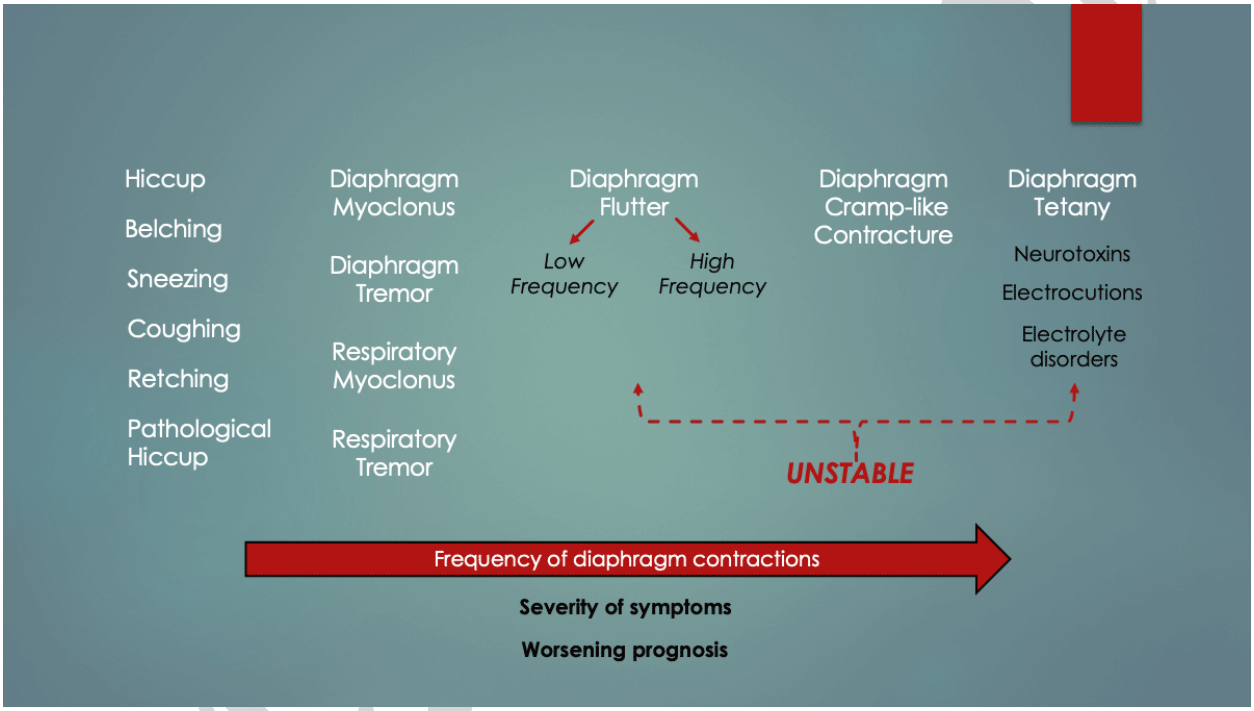
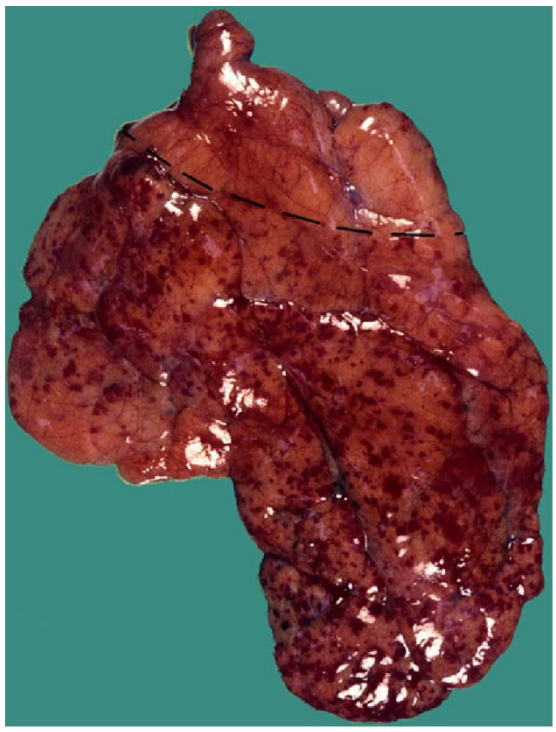


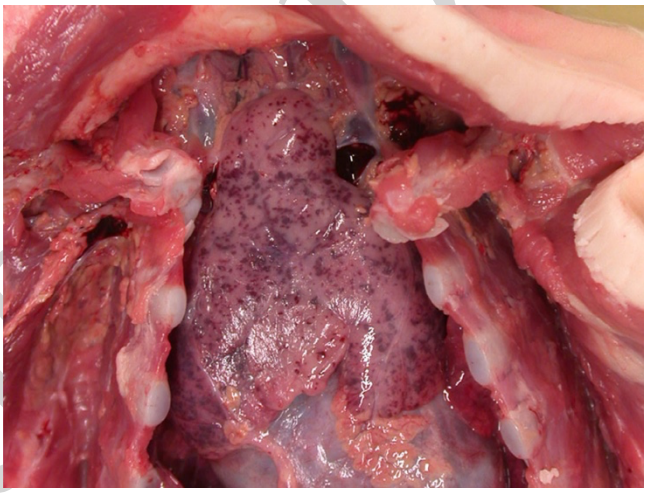
Figure 3 – Thymus Gland in Asphyxia. **A)** Beckwith's sign. The inferior, larger portion of the thymus is anatomically situated within the thoracic cavity whereas the smaller, superior segment is not (interrupted line). Sharp increase in the number of Tardieu petechial hemorrhages in the intrathoracic segment. **B)** Neonatal thymus (atop the heart) with Tardieu petechiae.

A)



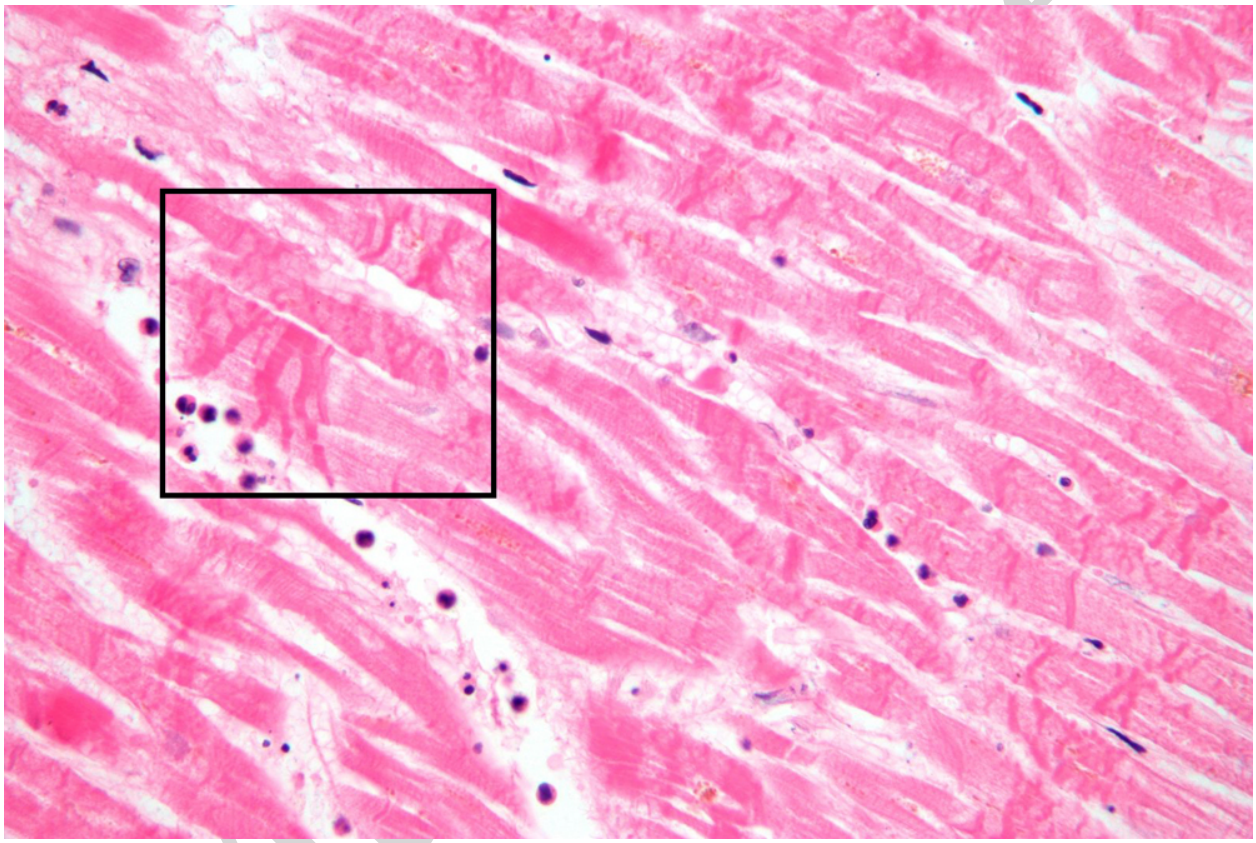
Courtesy of Prof. Roger W. Byard.
In "Sudden Death in the Young", 3rd Ed.
Cambridge Univ. Press 2010.

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 4 – 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 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 DCC.

Sleeping children need our help.

2. *Supplementary Table S1*

Table S1 – Differential Diagnosis of Case Patient's Symptoms. Causes of pediatric rib pain and apnea are listed separately (A, B) 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.

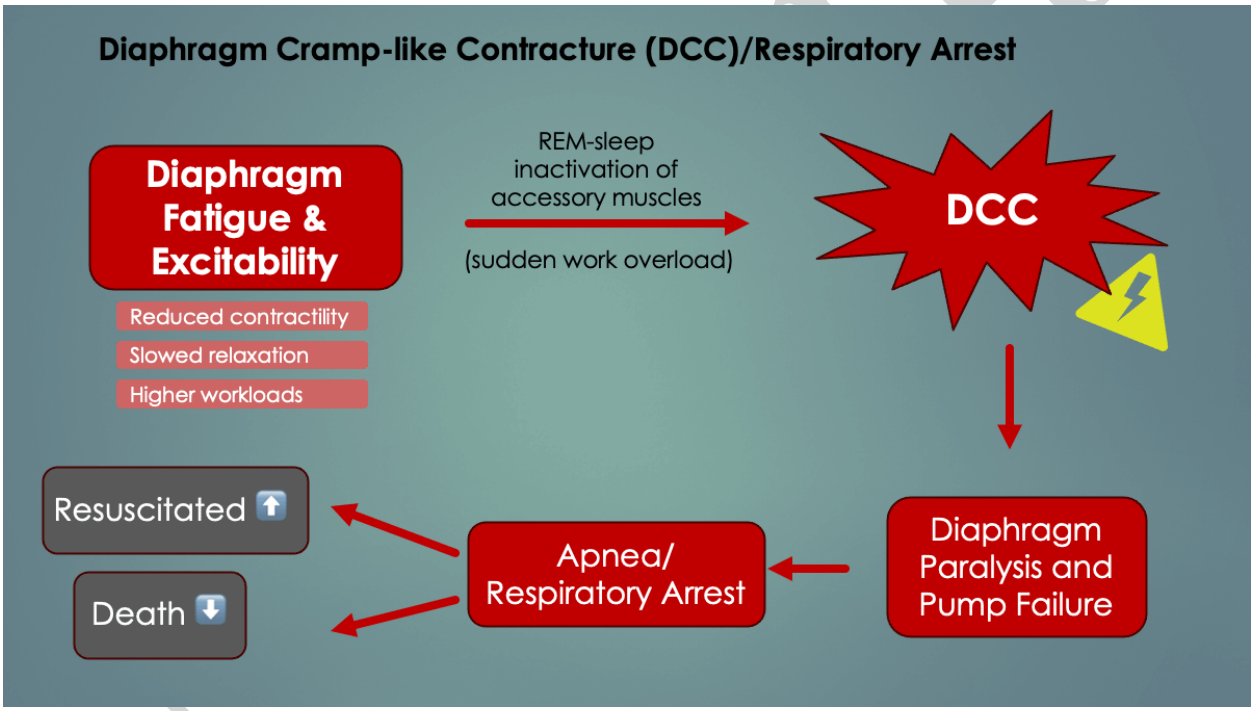
A. Unilateral and Bilateral Pediatric Rib Pain*		**Apnea?**	**Recurrent?‡**
	Rib fracture, muscle strain, intercostal neuralgia	No	Possible
	Fibromyalgia, juvenile rheumatoid arthritis	No	Possible
	Pleurisy, pleurodynia	No	Possible
	Tumours of chest wall and ribs	No	Unlikely
	Pneumothorax, pneumomediastinum	No	Unlikely
	Electrical injury	**Possible**	**Possible**
	Panic attack, somatoform and fictitious disorders, malingering	**Possible**	**Possible**
	Child abuse	**Possible**	**Possible**
	Intercostal muscle cramp	**Possible**	**Possible**
	Diaphragmatic cramp-like contracture	**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	**Yes**	**Possible**
	Diaphragmatic cramp-like contracture	**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 contracture		**High**

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

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

3. Supplementary Figure S1

Fig. S1 – DCC/Respiratory Arrest Flow Diagram. DCC is thought to be triggered by work overload in a fatigued diaphragm when the respiratory accessory muscles (RAM) are inactivated by the CNS in REM-sleep. Respiratory arrest can be reversed by rescue breaths, but the window of opportunity is short given hypoxic cardiac arrest will occur within 3-5 minutes.



4. Supplementary Figure S2

Fig. S2 – Thymus Gland in Asphyxia. 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. *Courtesy of Prof. Roger W. Byard. In "Sudden Death in the Young", 3rd Ed. Cambridge Univ. Press 2010.*