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

Abstract

The diaphragm is the primary muscle of respiration. Here, we disclose a fascinating patient's perspective that led, by clinical reasoning alone, to a novel mechanism of spontaneous respiratory arrests, termed, diaphragm cramp-contracture (DCC). Although the 7-year-old boy survived its paroxysmal nocturnal "bearhug apnea" episodes, essentially by breathing out to breathe in, DCC could cause sudden unexpected deaths, especially in infants because of underdeveloped, untrained respiratory muscles. Diaphragm fatigue is central to the DCC hypothesis in SIDS. Most, if not all, SIDS risk factors contribute to it, namely prone position, rebreathing, nicotine, overheating and infections. A workload surge by a roll to prone position or REM-sleep inactivation of airway dilator or respiratory accessory muscles can suddenly trigger excitation. Electromyography studies in preterm infants already show that diaphragm fatigue and temporary failure by transient spasms cause apneas, hypopneas and forced expirations, all leading to hypoxemic episodes. By extension, prolonged spasm as a diaphragm cramp would induce sustained apnea with consequent severe hypoxemia and cardiac arrest if not rapidly aborted. This would cause a sudden, rapid, silent death consistent with SIDS. Moreover, a unique airway obstruction could develop where the hypercontracted diaphragm resists terminal inspiratory efforts by the accessory muscles. It would disappear postmortem. SIDS autopsy evidence consistent with DCC includes myofiber disruptions and anoxic contraction band necrosis as well as signs of agonal breathing from obstruction. Screening for diaphragm injury by myositis, myopathy and excitation include serum CK-MM and skeletal troponin-I. Excitation could be visualized on ultrasound or fluoroscopy and monitored by respiratory inductive plethysmography or electromyography.

CPAP: continuous positive airway pressure, D-EMG: diaphragm electromyography, DCC: diaphragm cramp-contracture, DD: diaphragm dysfunction (fatigue or insufficiency), DP: diaphragm paralysis, Edi: electrical activity of diaphragm, HE: hypoxemic episode, HHVD: hypoxemic/hypercapnic ventilatory depression, IAM: influenza-associated myositis, ICM: intercostal muscles, IVC: inferior vena cava, MV: mechanical ventilation, OSA: obstructive sleep apnea, PH: pulmonary hypertension, RAM: respiratory accessory muscles, RIP: respiratory inductive plethysmography, RSV: respiratory syncytial virus, SIDS: sudden infant death syndrome, SUDC: sudden unexplained death in childhood, SUDEP: sudden unexpected death in epilepsy

Introduction

This is an informal version of the 2024 Diaphragm Cramp-Contracture (DCC) review paper coauthored by Dr. Eisenhut and I, soon to be published in *Diagnostics* medical journal (Basel, Switzerland). With clickable links, it contains the same material but also includes all supplementary materials.

Dr. Eisenhut is a practicing pediatric consultant in Luton, England. We teamed up in 2023 after I had contacted him about his published report on an important RSV bronchiolitis case. I am a former board-certified emergency department physician with over 15 years' clinical experience, currently practicing at a medical walk-in clinic in Toronto, Canada. I completed my residency training in emergency medicine in 2005 (Grand Rapids, MI, USA). Before completing medical school in the late 90's at the University of Queensland (Brisbane, Australia), I obtained a master's degree in pathology at McGill University (Montreal, Canada). I had no idea then how helpful this education (and ER practice) would become.

In early 2023 a patient shared a fascinating medical history suggesting the existence of a previously unrecognized mechanism of spontaneous respiratory arrests in children, which was termed, novel diaphragm cramp-contracture (DCC) [1]. While he survived its repeated paroxysmal nocturnal "bearhug pain apneas", DCC could be fatal, especially in infants. After two years of full-time literature review, writing and communications, and despite remaining skeptical throughout, we have come to suspect DCC as a terminal pathologic mechanism in many *non-arrhythmogenic* sudden unexpected deaths. This includes those in infants (SUDI, including SIDS), older children (SUDC), epilepsy (SUDEP) as well as some sudden cardiac deaths (SCD) and even severe abdominal winding injuries. In addition, it appears transient diaphragm spasms in preterm infants contribute to forced expirations, apneas-hypopneas and periodic breathing, all of which are known to cause recurrent hypoxemic episodes that are associated with serious long-term morbidity and mortality (including SIDS and SUDC). The same could induce breath-holding spells in older children as well as sleep-disordered breathing at all ages, including some obstructive and "central" sleep apneas. Those too are associated with major cardiovascular disorders occurring over the long term, such as hypertension, arrhythmias and SCD.

We realize such sweeping statements appear grandiose; however, please bear with us given young lives are at stake and we can do something about it now. That is the purpose of this paper. Here we present how we arrived at DCC (and diaphragm spasms) and provide supporting evidence so that you can decide for yourself.

**Patient "0" – Caucasian 52-Year-Old Healthy Male**

Though an adult at presentation, the 52-year-old case patient shared a harrowing story of painful nocturnal respiratory arrests that sporadically afflicted him throughout his childhood and youth. He felt he came within a breath of losing his life each time. Starting at 7 years old one night, he suddenly awoke gasping (mouth opened involuntarily, unable to inspire) with bilateral rib pain that felt like someone had picked him up from behind in a tight bearhug. The pain was characterized as pleuritic and cramp-like in nature. He did not recall being ill at the time or sharing the bed, however, did have many risk factors overlapping with those identified in SIDS (e.g., household cigarette smoke, cold climate, nocturnal sweating, deep sleeper with tendency to pull blankets over shoulders and head and a history of severe gastroesophageal reflux [2], requiring hiatal hernia repair at age 18 months of age). When he tried inspiring forcefully, it was met with more pain and complete resistance to airflow. Realizing it was futile he experimented — as only a young child can despite the duress of nearing death — learning he could still exhale. Forced inspirations again futile, he feels he then saved his life by exhaling, followed quickly by three short burst (staccato), high-pressure inhalations "like a pilot breathing in a centrifuge" (**Video 1**). Immediately the pain and obstruction disappeared, and normal breathing resumed. He then went back to sleep as if nothing had happened. With sporadic recurrences over the next ten years, always at night while asleep, he reemployed this breathing technique and even learned to do it in his sleep. He commented, "Over the years I became intricately aware of this thing, fearing the pain and inability to breathe, learning to abort it by recognizing its [prodromal painful rib fasciculations] and quickly taking in a breath before the big pain would kick in [at end-inspiration]" (obviating the need for the rescue breaths). As he grew older, he, "just assumed this happened to everybody", perhaps minimizing the traumatic events as a psychological defense mechanism. Sadly, he never told anyone until 45 years later. For more details, see **Patient's Perspective** in *Supplementary Materials*.

Although beyond the scope of this paper, most items in the differential diagnosis (**Supplemental Table 1**) were easily excluded using clinical reasoning of key historical features: spontaneous sudden-onset recurrent nocturnal cramp-like bilateral rib (bearhug) pain with complete inspiratory arrest. The most common causes of nocturnal respiratory distress in children, such as panic attacks, sleep paralysis, night terrors, seizures, bronchospasm, laryngospasm and OSA were ruled out simply because they do not feature intense pain. Similarly, painful conditions of the ribs or chest do not include a 100% airway obstruction. This left the novel diagnosis of bilateral cramps of the diaphragm and intercostal muscles (**Figure 1**). [Alternatively, the entire story could have been fictitious or related to child abuse (both denied). However, the patient's account was exceptionally

detailed and remained consistent throughout, supporting his authenticity and credibility.] Given it is possible a cramp might localize to a region within a muscle body, yet apnea occurred (failure of the entire inspiration movement), it was necessary to introduce the term *contracture*. Thus, diaphragm cramp-contracture was adopted. <u>It was hypothesized that loss of diaphragm mechanical pump function by DCC induced a state equivalent to acute bilateral diaphragmatic paralysis</u> (explaining the patient's inspiratory arrest).

Why this is medically unheard of could relate to extremely high mortality (few survivors). Also, if there are any, they would be preverbal children unable to describe symptoms or older ones, like the case patient, who repressed or were reluctant to share memories. Lastly, it occurs during deep sleep, making recall and differentiation of reality from dreaming less clear. **Supplemental Table 2** provides further details on how DCC might have evaded detection historically.
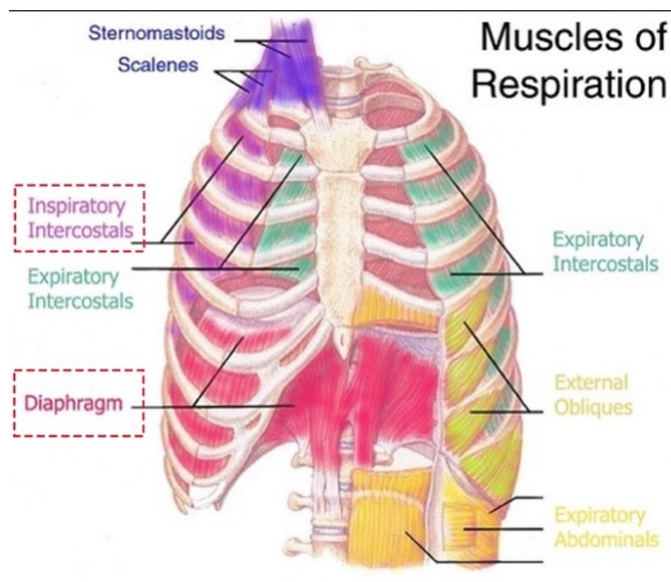
Figure 1 – Muscles of respiration. The primary inspiratory muscles are the diaphragm and paired groups of left and right external intercostal muscles (ICM, lavender). The latter reduce diaphragmatic workload in adults by their bucket handle movements which basically widen the ribcage. Theoretically, if the bilateral ICM were to suddenly fail by cramping, apnea would not occur as long as the diaphragm continued functioning (because it is the main inspiratory muscle). Contrarily however, if the diaphragm fails, apnea and inspiratory arrest could ensue but only if the ICM are not able to independently resume ventilation. Therefore, for apnea to occur, both must fail.
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Evidence for Putative DCC in Medical Literature

Next, the SIDS and SUDC literature bodies were investigated, looking to rule out DCC. The search revealed *Poets' et al* (1999) [3] report on nine infants aged 1-6 months who had succumbed to SIDS and had basic home cardiorespiratory "memory monitor" recordings of their final moments (not including oxygen saturations). Identical to the case patient's report, <u>terminal gasping and inspiratory apnea had occurred</u> (bradycardia as well). The authors explained how gasping in mammals occurs when PaO_2 falls under 5 - 15 mmHg (normal

range in infants is 50 - 80 mmHg) and is elicited only by hypoxemia, not hypercapnia or acidosis. Because of the gasping and bradycardia, this suggested severe hypoxemia was already present before the monitors were alarmed (alternatively bradycardia can be cardiac in origin, however, is very rare in children). Potential causes of progressive hypoxemia included blunted chemoreceptor responses, hypoventilation and rebreathing exhaled gases.[*] In addition, ineffective gasping had also occurred terminally whereby efforts to inspire were unsuccessful in reestablishing airflow, normoxia and reversing the bradycardia. This indicated some form of airway obstruction existed; however, it has never been identified other than speculated over laryngo*spasm* or bronchos*pasm*.

Another crucial paper was by *Lopes et al* (1981) [4] who determined diaphragm fatigue existed in 12 of 15 otherwise healthy preterm infants at mean 19.9 ± 13.7 days age using surface electromyography (EMG) of the diaphragm and intercostal muscles (ICM). Moreover, two different patterns of response to fatigue were observed: as opposed to infants who recruited their ICM, apneas occurred in those that did not. Some infants with prolonged apneas required tactile stimulation (presumably to wake them to breathe), and failing that, short-term CPAP and even mechanical ventilation (MV). Normally during wakefulness, respiratory accessory muscle (RAM) recruitment, which includes the ICM, occurs by a process known as respiratory load sharing (or load dependence) wherein ventilatory workload is diverted from the diaphragm to the ICM as diaphragm fatigue sets in (and vice-versa) [5]. In fact, rib retractions, commonly observed in children with respiratory distress, provide a direct visual cue of ICM activation secondary to diaphragm fatigue.[†] EMG had determined the apneas involved simultaneous failure of both ICM and diaphragm (preceded by worsening fatigue), and it occurred only when ICM did not take over the work of breathing. The authors discussed the role of REM-sleep — when there is physiologic CNS inhibition of skeletal muscles including the ICM but not diaphragm — however, it could not be concluded because sleep state was not measured. Nevertheless, in extension of this line of interpretation, <u>it appears REM-sleep predisposed to the apneas, and they occurred by failure of both ICM and diaphragm</u> (that is, *peripheral* malfunction). Furthermore, those who had arousal, presumably by hypoxia- or hypercapnia-mediated

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[*] Rebreathing exhaled gases is a highly suspected SIDS risk factor that is worsened by prone position, bed sharing, soft linens and bed toys. This would lead to gradual hypoxemia as well as hypercapnia and respiratory acidosis. Improved bedroom ventilation by an open window or fan would reduce it. Indeed, both interventions appeared to be SIDS-preventative in a 2008 retrospective case-control study that interviewed mothers of SIDS victims and age-matched controls. Unfortunately, no follow up studies were done. Coleman-Phox K, Odouli R, Li DK. Use of a fan during sleep and the risk of sudden infant death syndrome. *Arch Pediatr Adolesc Med.* 2008 Oct;162(10):963-8. PMID: 18838649.

[†] Another physical sign of diaphragm fatigue (and outright failure) is paroxysmal breathing or thoraco-abdominal asynchrony. It also occurs in diaphragm paralysis and paresis whereby ventilation is powered or assisted by RAM contractions, respectively. With inspiration, the abdomen becomes drawn in instead of descending and expanding.

chemoreception, probably reactivated their ICM, thereby avoiding the apnea. What remains undetermined however, was the reason for the lack of arousals in others as well as the mechanism of diaphragm failure itself. **Figure 2** summarizes these findings and is consistent with other authors' conclusions [6-8]. Notably, if traditional sleep study chest impedance belts were used, these apneas would have been classified as central, because of absent respiratory movements.

In support of peripheral apnea in SIDS was evidence presented by *Siren and Siren* (2011) in their Critical Diaphragmatic Failure hypothesis (a review article). They postulated that several diaphragm fatiguing (and added workload) factors cumulatively increase the risk of diaphragm failure in SIDS, including non-lethal viral infections, prone positioning, male sex, hypoxia, hypercapnia, high altitude, bottle feedings as well as underdeveloped RAM and their inactivation in REM-sleep [8-11]. Others included hypomagnesemia, overheating and tobacco smoke. Importantly, all are SIDS risk factors. In support of DCC here though is the sudden and unpredictable nature of SIDS. Suddenness, without prodromal respiratory distress, is in support of a DCC event rather than gradual respiratory failure. Regardless, the *Lopes* group put it best in 1981, "The neural [CNS] basis for apnea is so deeply entrenched that it is difficult to accept that some apnea may be due to [peripheral] respiratory muscle failure".
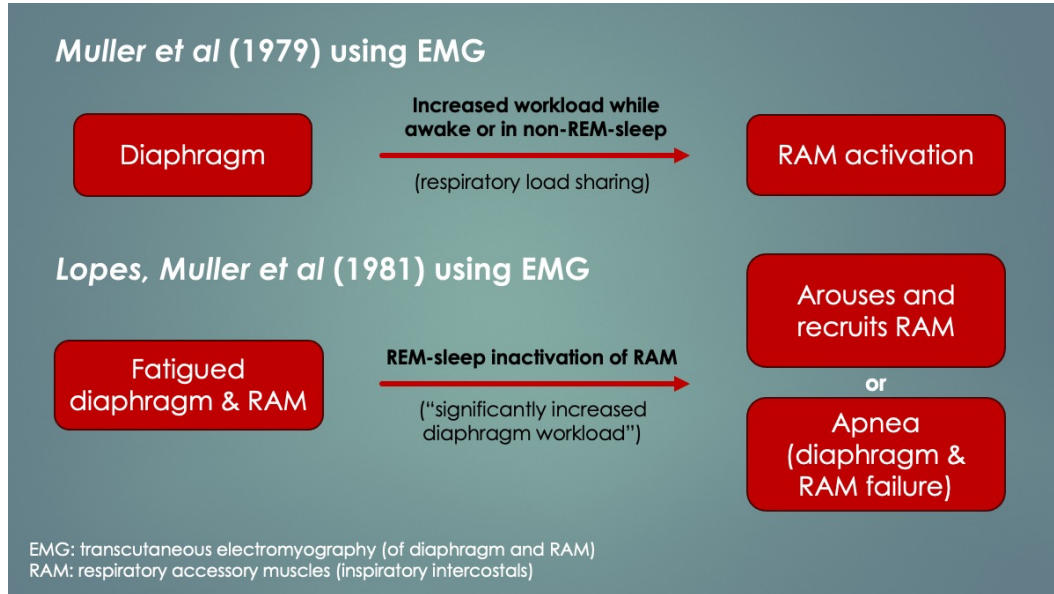
Figure 2 – Respiratory load compensation, REM-sleep inhibition and arousal-versus-apnea in infants with diaphragm fatigue. Normally under increased physiological demand or diaphragm fatigue, ventilatory workload is shared between the diaphragm and RAM, including the inspiratory intercostals. However, sudden RAM inactivation in REM-sleep leads to apneas related to the already present, and consequently worsening diaphragmatic fatigue (causing failure). Lack of arousal, with no consequent RAM recruitment, potentiates the apneas [4,5,6].
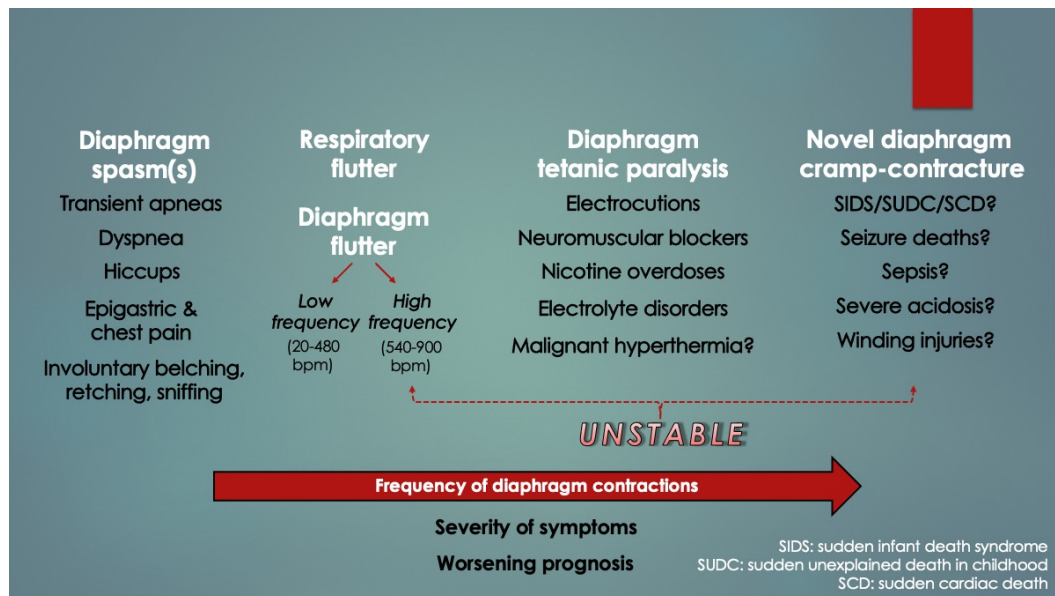
Diaphragm Hyperexcitability Disorders (DHD)

Further literature review revealed numerous contraction abnormalities of the diaphragm, most importantly, diaphragm flutter (van Leeuwenhoek's disease) [12] and respiratory flutter. Diaphragm flutter (DF), thought to be rare, involves rhythmic involuntary contractions of the diaphragm superfluous to those that occur with normal neural (CNS-mediated) autonomic breathing (as opposed to *volitional breathing* which involves a separate neuroanatomic pathway also carried by the phrenic nerves). Respiratory flutter denotes excitation of the accessory muscles such as the rectus abdominae and ICM in addition to the diaphragm. Immediately, its existence alone demonstrated how anatomically disparate groups of inspiratory muscles can simultaneously develop pathological excitation (supporting the hypothesis that cramping of both diaphragm and ICM caused the case patient's symptoms) [13]. In that paper, respiratory flutter in three full-term neonates was reported as an "underrecognized cause of respiratory failure" , diagnosed by respiratory inductive plethysmography (RIP) and/or fluoroscopy. Within hours of birth, all developed ventilatory distress involving stridor, grunting, rib retractions and inspiratory ratchetlike or fluttering chest movements requiring temporary CPAP or MV. Chlorpromazine, a typical antipsychotic medication, helped abate the flutter in all three. However, in another report, DF was well tolerated in three babies of mean 12-weeks' age (gestational age unknown) with bronchopulmonary dysplasia and respiratory syncytial virus (RSV) bronchiolitis. Notably, all are SIDS risk factors (including age), suggesting a possible link between flutter and SIDS [14]. Aside from postconceptional age though, it is unknown why there was such a difference in clinical presentations between the patients reported in the two papers.

Numerous case reports of other pathological excitation states (neuromuscular irritability) of the diaphragm were found on review, and these could be broadly classified under single contraction phenotypes (e.g., hiccups and spasms) or arrhythmias (e.g., low and high frequency flutter and fibrillation). Examples of such hereby termed "diaphragm hyperexcitable disorders" (DHD) in addition to hiccups, spasms, flutter and fibrillation were, diaphragmatic and respiratory tics, fasciculations, palpitations, myoclonus, tremor and belly dancer's dyskinesia. Summed up however, it can be seen in **Figure 3** that DHD appear to present along a frequency spectrum of worsening symptoms and prognoses. The higher the frequency, the more clinically unstable is the patient. This is a novel finding. DCC, which could represent a very high frequency DHD akin to tetany, might also belong to the spectrum, however, given extremely high mortality with few survivors, these cases would

have inadvertently been excluded by clinical studies (an inverse form of survivorship bias, or *mortality bias*).*

Figure 3 – Spectrum of diaphragm hyperexcitation disorders (DHDs). Polyonymous clinical descriptors and diagnoses upon literature review made it a challenge categorizing them. However, a pattern emerged: as the frequency of non-physiologic diaphragm contractions increased, respiratory distress became prominent, some with sustained apneas (respiratory arrest). Those to the right presented with severe respiratory distress or frank arrest and could be termed, "unstable diaphragmatic arrhythmias". DCC could belong to this spectrum. See Citations for Figure 3 in *Supplemental Materials. Click here to access an online data spreadsheet of our DHD literature review findings.*

Tobacco smoke exposure is a well-known SIDS risk factor. By contrast, nicotine overdoses in young children, even from ingesting snuff box scrapings died in under 30 minutes. The respiratory arrest was not centrally mediated [15]. Rather, it occurred by peripheral paralysis from a *sustained* diaphragm spasm (essentially a tetanic cramp-contracture) [16, 17]. Therefore, in infants exposed to subtoxic nicotine levels from household tobacco smoke, it is likely the threshold for diaphragm excitation is lowered (by respiratory muscle fatigue) [18].† Similarly, nondepolarizing neuromuscular blockers like succinylcholine, commonly used to facilitate endotracheal intubation, also induce

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* *"If you are studying a high mortality population, such as old people or people with AIDS, the people who survive and remain in your sample may be fundamentally different from the people who have already died."* The opposite also applies where those who died never had the chance of being researched, thus losing the opportunity to identify and study the disease. Source: Michael J. Rosenfield 2012. In Notes on terminology for evaluation of research. Stanford.edu. Available online.

† Cold climate is a well-known SIDS risk factor (winter peaks in deaths). Indoor tobacco smoke will rise to the upper level of the home. This is typically where children's bedrooms are located. Home heating would exacerbate this by concentrating smoke to the upper floor. Thus, home heating could be a major contributor to the climactic factor. Additionally, DHD could be more common in cold environments (*vide infra*).

peripheral respiratory arrest, therefore both were placed at the most severe position in the spectrum (under Diaphragm Tetanic Paralysis). In addition, some fatal electrocutions also occur by tetanic contractions of the respiratory muscles (not just cardiac arrhythmias), thus, this too was included [19, 20]. Deaths from severe metabolic acidosis (in diabetic ketoacidosis [21] and lactic acidosis [22]), malignant hyperthermia [23], botulism [24], rabies [25] and tetanus [26] also appear to occur by peripheral arrest, even sepsis too *(vide infra)*. By contrast, the heart also exhibits sensitivity to acidosis, as demonstrated by a decrease in threshold for ventricular fibrillation [27].

The etiologies of DHD are extensive and beyond the scope of this paper, however, it is important to note that pain and psychological distress are inciting causes at all ages [28]. Feeding young children can be difficult at times, sometimes requiring forced effort, and this strenuous activity has been associated with apneic, SIDS-like awake deaths [29]. Similarly, apneic hypoxemic episodes (HE) occurred with feeding in infants as well as with anger, handling and noxious triggers like pain, airway suctioning and loud noises [30, 31]. This is in striking similarity to life-threatening apneic-cyanotic HE reported in six infants with histories of recent seizures (suggesting a common mechanism with SUDEP; *vide infra*) [32]. All of this supports the notion that stress-induced diaphragm excitation could cause serious respiratory symptoms, sometimes fatal.*

Table 1 lists the various causes of respiratory muscle (Type II, hypercapnic) failure obtained by literature review. Importantly, it was recognized that diaphragm-related respiratory insufficiency and failure is an underrecognized cause of serious morbidity and mortality in all ages, ranging from fatal soft tissue injuries of the neck (acute bilateral phrenic neuropathies) [33] to heatstroke/hyperthermia [23, 34] and terminal COVID-19 infections (acute diaphragm myopathy) [35]. Other important causes include septic, hypovolemic and cardiogenic shock *(vide infra)*.

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* By extension, increased diaphragmatic muscular tone in high stress situations could physically squeeze on the traversing esophagus (and stomach), leading to the commonly experienced gastric symptoms of anxiety including "butterflies", epigastric discomfort, nausea, vomiting, belching and dyspepsia. This would represent a novel connection between mind and body.

Multi-organ (CNS, phrenic nerve(s), diaphragm, respiratory accessory muscles)		Onset	Side	RAM Involved	Citations
Electrocution	Lightning, low- and high-voltage shocks	S	Both	✓	[1,2]
Neurotoxin	Nicotine, botulism, tetanus, curare, organophosphates, carbamates, tetrodotoxin, strychnine, envenomations	S	B	✓	[3-5]
Medication	Neuromuscular blockers, aminoglycosides, catecholamines	S	B	✓	[6-8]
Electrolyte	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 – Etiologies of acute and chronic respiratory muscle paralysis and paresis leading to Type II hypercapnic failure. The CNS, phrenic nerve(s), diaphragm and/or RAM may be involved. Insults can be sudden or gradual in onset, bilateral or unilateral and neurologically complete (paralysis) or incomplete (paresis). Diaphragm fatigue, that is, temporary weakness reversed by rest, worsens clinical course for most chronic conditions in which mortality typically occurs by acute respiratory failure. Diaphragm failure is an underrecognized cause of mortality in all ages, such as by cervical phrenic nerve injuries, low-velocity blunt abdominal trauma (severe winding injuries) and possibly restraint cardiac arrests, cold-water submersions and some drownings (especially those shoreside in cold water or in known strong swimmers) [1]. See Citations for Table 1 in *Supplemental Materials*.

Categorization could be made by organ involvement (CNS, phrenic nerve(s), diaphragm or accessory muscles) as well as laterality, rapidity of onset and degree of weakness (complete paralysis versus paresis). For example, whereas some electrical injuries and cervical spine transections induced simultaneous, sudden and complete bilateral paralysis of both diaphragm and RAM, isolated diaphragm weakness occurred by direct abdominal trauma or phrenic nerve injuries (e.g., nerve tractions in birth trauma or chiropractic manipulations). In the very young (neonates), acute bilateral diaphragm paralysis (DP) despite functional RAM, induced critical Type II failure that was followed within minutes by cardiac arrest and death unless reversed by ventilatory support [36, 37, 38]. This supports the argument that the very young, functional RAM cannot independently ventilate the lungs (when the diaphragm is inactivated). However, older infants survived probably because their maturing RAM tolerated the added workload. This also provides a compelling

explanation why infants aged 2-4 months are at highest risk for SIDS (and not older): underdeveloped, weaker RAM. Older infants have had time for RAM maturation by load-dependent recruitment and training. With this classification scheme it became evident that acute DP can be immediately fatal when it is bilateral, neurologically complete and occurs in those with weak, paralyzed or cramped RAM (**Figure 4**). Also, apnea duration needs to be sufficient as to induce critical hypoxemia and secondary cardiac arrest (only 1-2 minutes) [39]. These too are novel findings. Death by DCC in young infants satisfies these criteria because the RAM are weak and the effective DP is bilateral and probably complete (i.e., diaphragm fully inactivated by contracture). It is also paroxysmal (sudden and unexpected), just like SIDS and many other child deaths. Lastly, the process is silent, rapid and unwitnessed in most cases (obviating resuscitation efforts).
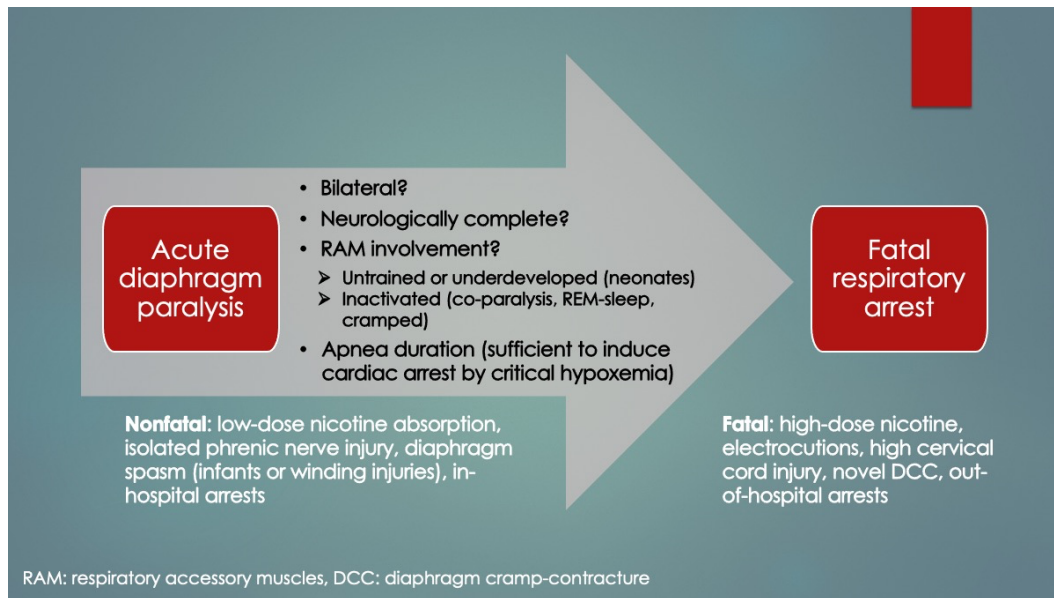
Figure 4 – Criteria for fatal respiratory arrests by acute diaphragm paralysis, with examples.

Table 2 similarly lists the causes of diaphragm fatigue (and increased ventilatory workloads) in infants ascertained upon broad literature review. Importantly, most, if not all, are known SIDS risk factors (or closely relate to them). It should also be pointed out that as opposed to diaphragm weakness, diaphragm fatigue is reversed by rest. Diaphragm fatigue or dysfunction (DD) is also referred to here as diaphragm insufficiency.

A) Increased diaphragm workload	Citation	B) Diaphragm fatigue/excitation factors	Citation
Prematurity/low birth weight (underdeveloped, weak RAM)	[1]	Prematurity/low birth weight (reduced fatigue-resistant, Type 1 myofibers)	[1]
Compliant ribcage (distortion upon inspiration)	[1]	Household tobacco smoke (nicotine)	[32-34]
Male gender	[2-6]	Overheating & diaphoresis	[35-38]
Prone position	[7,8]	Infections (gastroenteritis, URI, sepsis)	[39,7]
REM-sleep RAM inactivation and OSA	[7,9-11]	Fever, dehydration	[18-22]
Bronchiolitis and pneumonia (atelectasis, infiltrates)	[12,13]	Viremia, bacterial toxins, skeletal muscle myositis/myopathy	[40-43]
Bronchopulmonary dysplasia	[2,14,15]	Septic shock	[19,20,44,45]
Laryngospasm, bronchospasm	[16,17]	Metabolic acidosis (tissue hypoxia, hypovolemia, stool bicarbonate loss)	[21,46-48]
Dehydration, hypovolemic shock	[18-22]	Rebreathing exhaled gases, hypoventilation	[1,49-52]
Anemia of infancy, hemorrhage	[23-25]	Hypoxemia	-
Bottle feeding	[26,27]	Hypercapnia	-
Psychological distress, pain	[27-29]	Respiratory acidosis	-
Pacifier weaning?	[30,31]	Seizures (focal and generalized)	[53-56]

RAM: respiratory accessory muscles, OSA: obstructive sleep apnea, URI: upper respiratory infection, Italics: putative (unproven)

Table 2 – Diaphragm workload- and fatigue/excitation factors in infants. The fatigued diaphragm is prone to neuromuscular excitation by work overload from a variety of endogenous and exogenous causes. Many are SIDS risk factors. Premature, smaller infants have incompletely developed respiratory muscles as well as less fatigue-resistant diaphragm myofibers. A) Higher ventilatory workloads occur in neonates than older infants because of a collapsible, unstable chest wall. Ultrasound evidence suggests the male diaphragm works harder and fatigues easier than in females (*vide infra*). Prone positioning, REM-sleep, obstructive sleep apnea (reduced supraglottic patency) and respiratory infections all add workload as does anemia of infancy by a reduced oxygen-carrying capacity. Bottle feeding and psychological distress are known to trigger hypoxemic episodes. Pacifiers are SIDS-preventative, possibly digit-sucking too. Both might reduce workload. B) Nicotine induces skeletal muscle excitation *ex vivo* whereas an overdose causes fatal respiratory arrest by diaphragm paralysis. Similarly, fever, acidosis and loss of hydration and electrolytes all impair contractility and delay muscle relaxation leading to diaphragm fatigue, increased tone and excitability. In children with RSV or influenza-B calf myopathy, the diaphragm might similarly be affected. Bacterial toxins in sepsis directly impair diaphragm contractility and delay relaxation leading to fatal respiratory arrests. Hypoxia, hypercapnia and respiratory acidosis from CO_2 rebreathing and hypoventilation also reduce contractility and relaxation. Hypercapnia and hypoxemia both reduce alveolar ventilation, thereby exacerbating both conditions in positive feedback cycles. Seizure-induced diaphragm excitation carried by phrenic nerves induces fatigue and terminal apnea in mice. See Citations for Table 2 in *Supplemental Materials*.

Diaphragm Excitation in Infants with Respiratory Instability

The greatest pathologic threat to infants is respiratory, and sleep is an especially vulnerable state. This is particularly concerning not only because they disproportionally spend their time sleeping, but most of it is active (REM) sleep, a stage associated with more respiratory instability. In living infants this is observed as transient apneas and hypopneas (shallow breaths) as well as periodic breathing, increased arousals and HE. Recurrent HE predispose to serious long-term morbidity such as cerebral palsy, retinopathy, blindness, deafness, poor growth, neuro-developmental delays and pulmonary hypertension with cardiomyopathies. Mortality is higher, including by sudden respiratory arrests in RSV bronchiolitis [40] and sudden unexpected deaths even as late as 18 months of age, if not longer (SIDS and SUDC, respectively) [41]. It is also more common in those with chronic

conditions such as bronchopulmonary dysplasia, cerebral palsy and neuromuscular disease, like muscular dystrophies and congenital myopathies.

Some HE are not visually apparent, whereas others may exhibit cyanosis, hypotonia, loss of consciousness or seizures. Simultaneous behaviours include *silent* squirming, kicking, grimacing, writhing and bearing down, sometimes followed by hiccups (diaphragmatic contractions) [30]. Unusually, these behaviours are associated with crying, so the silence supports the case patient's report that inspiratory arrest had occurred. This is corroborated by the work of *Southall et al* (1990) [31] who found prolonged absence of inspiratory efforts was common among 51 infants with recurrent cyanotic HE. Expirations still occurred, also consistent with our case.

Defined as oxygen saturations under 88% for over 10 seconds, HE in one study lasted from tens of seconds to two minutes, occurring up to hundreds of times daily in spontaneously breathing former-preterms at 44 ± 21 days of age [42]. They even occur in infants receiving mechanical ventilation, as exhibited by forced expirations, hypopneas and reliance on ventilator breaths associated with doubling of pulmonary resistance and reduced lung compliance of unknown origin (also, simultaneous increases in gastric and esophageal pressures) [43].

Respiratory instability is thought to be caused by abnormal chemoreception and immature development of the neural control of breathing, worsened by underdevelopment of the lungs (primarily, surfactant deficiency). However, some HE appear to occur by voluntary abdominal muscle contractions (forced expirations), sometimes followed by breath-holding (short apneas) [44, 45]. As seen in **Figure 5,** an abnormal respiratory waveform manifests: a prolonged expiration (or prolonged expiratory apnea). Importantly, this occurs just at the end-expiration phase of the respiratory cycle (identical timing to DCC onset as reported by our patient).
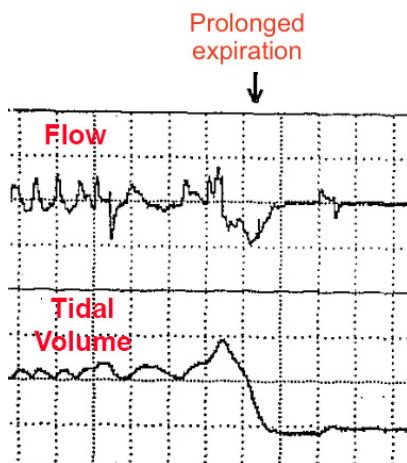
Figure 5 – Prolonged expiratory apnea in an infant. The apnea (seen as flatlines in both flow and tidal volume waveforms) was preceded by a big expiration with a decrease in lung volume. Typically, this is followed by a hypoxemic episode (transient oxygen desaturation).

Curiously, almost nothing is mentioned in this literature about the vital muscles that power respiration despite compelling reports from the late 70's indicating infants were "very close to the threshold of fatigue" [and failure] [6]. Diaphragm fatigue occurs by a number of factors unique to very young compared to older infants: (1) highly compliant, cartilaginous ribcage which reduces ventilatory efficiency, (2) less efficient RAM contributions because of less conditioning and anatomical differences (worsened in REM-sleep by CNS inhibition), (3) decreased range of pump displacement due to diaphragm flattening, (4) fewer fatigue-resistant, slow-twitch diaphragm myofibers, and (5) lower total cross-sectional area of all myofiber types [46]. Also, at any age, anything that increases work of breathing, like REM-sleep, a roll to prone position, pain, psychological distress, forced bottle feedings, laryngospasm, bronchospasm or pulmonary infections exacerbates the fatigue, even sepsis and severe acidosis too (evident as *Kussmaul's* hyperpneic, laboured respirations to "blow off" CO_2). The latter two also directly impair diaphragm contractility and relaxation (*vide infra*). In addition, anemia of infancy, a known risk factor for apnea of prematurity [47], breath-holding spells [48] and apparent life-threatening events in young children [49], could explain these apneas simply because the reduced blood oxygen-carrying capacity exacerbates DD, particularly under times of increased physiologic demand. Clearly, the causes of DD-induced respiratory instability in infants (and proposed ventilatory failure) are complex and multifactorial, in keeping with the host of events thought to lead up to a sudden unexpected infant death.

Another held mechanism of HE is hypoxic (and hypercapnic) ventilatory depression (HHVD). This process, exacerbated in REM-sleep, is thought to be from central causes. Normally, the compensatory ("CNS feedback") response to hypoxemia or hypercapnia in mammals occurs by an increase in minute ventilation (or V_E = respiratory rate x tidal volume). This happens in both adults and infants but after an initial 1-2-minute compensatory increase in infants (and about 20 minutes in healthy adults, depending on degree of hypoxia or hypercapnia), it is suddenly decreased (or *depressed*) by a reduced respiratory rate. It has been a mystery why this presumed neural response is dysfunctional. Instead, it hereby appears HHVD might actually be caused by the reduced work output of diaphragm fatigue (insufficiency). It just takes longer to appear in adults because their mature, conditioned respiratory muscles are less vulnerable to fatigue. The pathological process is simple: persistent hypoxia or hypercapnia (e.g., from hypoventilation or rebreathing exhaled gases) combined with acidosis (from both respiratory and metabolic types) induce DD, leading to reduced alveolar ventilation which further compounds the hypoxia, hypercapnia and respiratory acidosis in positive feedback cycles. The slow onset yet progressively worsening hypoxia of an unstable DD feedback cycle during sleep would

explain the hypoxemic gasping seen in the *Poets'* SIDS victims (where critical hypoxemia preceded gasping, bradycardia and apnea alarms) [3]. As we shall see, repeated HE by this mechanism could be responsible for myopathic changes seen in the diaphragms of SIDS victims.

   In vivo analyses of ventilatory mechanics have determined that the dysfunctional drop of respiratory rate in HHVD occurs by a prolongation of the *expiratory phase* (T_E) of the breathing cycle. This too is thought secondary to CNS immaturity. However, in hamster diaphragm strips *ex vivo*, *Esau* (1989) [50] determined both hypoxia and hypercapnia reduced diaphragm contractility and slowed the *muscle relaxation phase* (T_R) of diaphragm contraction. By extension, this could be responsible for the delayed T_E. Similarly, *Herve et al* (1988) [51] found in rat diaphragm strips that increased workloads as well as ryanodine, an inducer of muscle fatigue, both delayed T_R. And when overloaded by ryanodine, contractility was markedly lowered, and a diaphragm *contracture* developed (excitation). Nicotine exerts a similar effect in toxic doses [16,17]. Although not reproduced *in vivo*, intact diaphragms might also be prone to contracture when T_R becomes longer than T_E (spasms and cramps). This could occur in a fatigued diaphragm working under high respiratory rates and ventilatory workloads (both common in illness), when it is unable to fully relax and return to its original resting position in time for the next breath. Literature evidence supporting this notion was limited; however, **Figure 6** demonstrates an example. There is an upwards wander in the chest impedance (tidal volume, V_T) baseline with air trapping (hyperinflation). It occurred in a spontaneously breathing preterm infant immediately after a short apnea associated with silent squirming and a spike in surface EMG activity thought to be from abdominal contractions. Instead, a diaphragm spasm could have been responsible. By comparison, air trapping in spontaneously breathing individuals does happen in COPD, asthma and interstitial lung diseases; however, does not apply here given the patient's age.
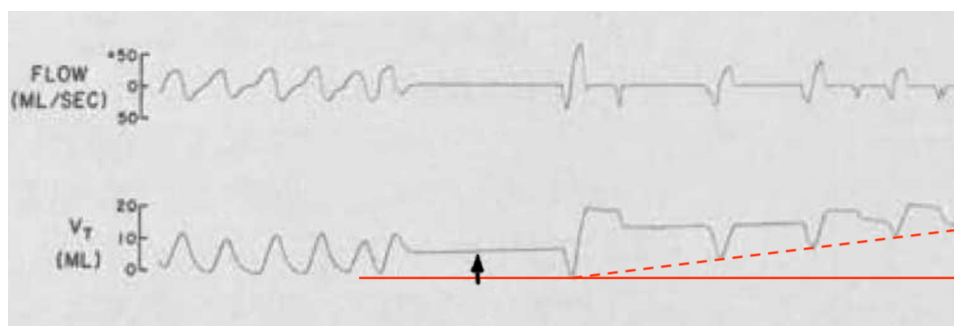
Figure 6 – Sleep polysomnograph demonstrating air trapping (breath stacking), hyperinflation and slowed, *reversed respirations* after an unidentified apneic event in a spontaneously breathing infant.

Normal tidal breathing was interrupted by a brief apnea (arrow) associated with silent squirming. It was followed by a stepwise, breath-to-breath increase in end-expiratory volume consistent with breath stacking (compare broken red line to solid red, tidal breathing baseline). Unusually, these respirations were slowed and reversed, in which expiration preceded inspiration (seen in the airflow tracing). All such changes were associated with persistently increased esophageal pressure for 44 s (not shown), thought secondary to voluntary abdominal muscle contractions (measured by *surface* EMG). Instead, diaphragm spasm could have been responsible, cross contaminating the EMG. The full image can be seen in **Supplemental Figure 1**. *Reprinted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved.* [30]

Along with hypoxia, hypercapnia, ryanodine, fatigue and possibly nicotine, both acidosis and endotoxins of *S. Pneumoniae* and *E. Coli* have been found to also prolong diaphragmatic T_R, precipitating diaphragm contracture *ex vivo* [50] and further fatigue *in vivo* [52]. This could be important not only in causing respiratory instability in infants with bacterial infections, but also sudden respiratory arrests in SIDS, SUDC and all other age groups. Both respiratory- and metabolic acidosis in children (the latter, for example, due to hypovolemia/shock as well as upper respiratory infections and diarrhea-associated bicarbonate loss) [53] overlap with SIDS risk factors including intercurrent infections, dehydration, fever and overheating. They could manifest in deadly fashion at the diaphragm by sudden respiratory failure from contracture. In fact, _extreme acidosis and hyperkalemia at SIDS autopsies were reported in a 2006 online Medscape article, but unfortunately were never confirmed_ [54]. Electrolyte disorders can affect the diaphragm much in the same way as the examples above, by inducing fatigue, but in this case from excitation-contraction coupling dyshomeostasis. The author went on to mention how critical acidosis could have developed in the days preceding the deaths. Both disorders were also identified in a report of 20 infants with idiopathic postneonatal apnea occurring in association with hypomagnesemia [55]. The sickest ones demonstrated bradycardia, acute respiratory distress and *skeletal muscle hyperirritability*; however, the diaphragm was not investigated. That author later went on to suggest hypomagnesemia causation in SIDS. Severe hypokalemia too is a known cause of respiratory muscle paralysis leading to asphyxiation [56]. Finally, parenteral nutrition, commonly administered to undernourished neonates, carries a risk for metabolic acidosis [57], and thus potential for diaphragm fatigue/excitation. In summary, it appears hypoxia, hypercapnia, acidosis, endotoxins, electrolyte disorders and nicotine all intersect at the diaphragm in infants, altering breathing mechanics (reduced contractility and delayed relaxation), culminating in fatigue and excitation in the form of spasms and cramps with consequent apneas and other forms of respiratory instability leading to HE.

Like the limbs, the diaphragm is composed of skeletal muscle. Fatigued skeletal muscles develop increased tonicity and neuromuscular excitation under increased workloads, commonly experienced when one is unfit, dehydrated or overheated [58]. Examples of excitation *in vivo* include twitches and fasciculations, spasms and cramps (sustained spasms), myoclonus (short arrhythmic spasms) and arrhythmias like flutter and fibrillation (which are well known to affect the heart). Pathological excitation of respiratory muscles has already been described, as evidenced by diaphragmatic and respiratory flutter. Importantly, whereas apnea from diaphragm spasm is not life-threatening because of its transience, that from a sustained cramp could be. With persistent diaphragm cramp-contracture in an infant, severe hypoxemia would ensue, causing sudden hypotonia, cyanosis and possibly seizure followed by bradycardia and cardiac arrest and death if not rapidly aborted. Unlike the 7-year-old case patient who autoresuscitated by troubleshooting and learning to breathe *in reverse*, infants may not be capable of such a counterintuitive task, thus a cardiopulmonary emergency could arise. Finally, whereas limb cramps can be aborted by stretching, this is clearly not possible with the internally located diaphragm. However, it is interesting to consider how the patient's rescue breaths might have terminated his DCC. Perhaps the rapid combination of expiration-inspiration forced the diaphragm to initially recoil cranially then quickly stretch as it moved caudally with inspiration, thereby overcoming the contracture tension and returning to normal function.

In infants with respiratory instability from diaphragm fatigue, diaphragmatic spasms with consequently delayed relaxation (akin to prolonged cardiac repolarization in diastole after a premature ventricular contraction) are hereby proposed to cause the observed forced expirations and breath-holding pauses, respectively, along with hypopneas and prolonged apneas. Diaphragm spasms would mimic abdominal muscle contractions seen on surface EMG. They too could increase esophageal and gastric pressures (diaphragm moves cranially, thereby reducing thoracic volume). This is supported by the diaphragm/RAM-induced apneas of the *Lopes* study [4] and provides an alternative explanation of HE, ridding any notion of a voluntary or behavioural component to forced expirations and breath-holding. It is also more intuitive given it is unlikely an undernourished, feeble preterm infant would be capable of persistently tensing their abdomen, in one instance for over two minutes, to the point of dropping their oxygen saturations below 75% [42]. Diaphragm spasms could also explain the silent nature of HE, simply because an inspiration cannot be taken while the organ is inactivated. Furthermore, the pain of spasm would explain the grimacing, writhing and kicking. Finally, this provides a solid foundation to hypothesize that persistent spasm, or diaphragm cramp-contracture, could be responsible for non-arrhythmogenic sudden unexpected deaths in infants (and possibly other ages too).

It follows then that periodic breathing also involves fatigue of the diaphragm that becomes temporarily dependent on the accessory muscles to maintain ventilation until reversed by rest (and vice versa by load sharing). Specifically, cyclical episodes of diaphragm fatigue, work overload and consequent spasms with transient inactivation followed by load compensation by RAM activation and then RAM fatigue and spasms, would give rise to a repetitive sequence of hyperpneas (from diaphragm spasm), hypopneas with paradoxical breathing (by independent RAM contractions while diaphragm is temporarily inactivated) and apneas (simultaneous failure of both diaphragm and RAM) commonly observed and as seen in **Figure 7** [59]. *Seppä-Moilanen* (2019) [60] determined periodic breathing was substantially reduced with supplemental oxygen and caffeine in 21 preterm infants. Apneas were also reduced in frequency. Both interventions may have improved diaphragm function directly rather than by centrally mediated effects. *Aubier* (1989) flatly summed this up, stating, "It is clear that the majority of chest physicians have emphasized disorders of the lung or abnormalities of ventilatory control *while ignoring the muscles*".
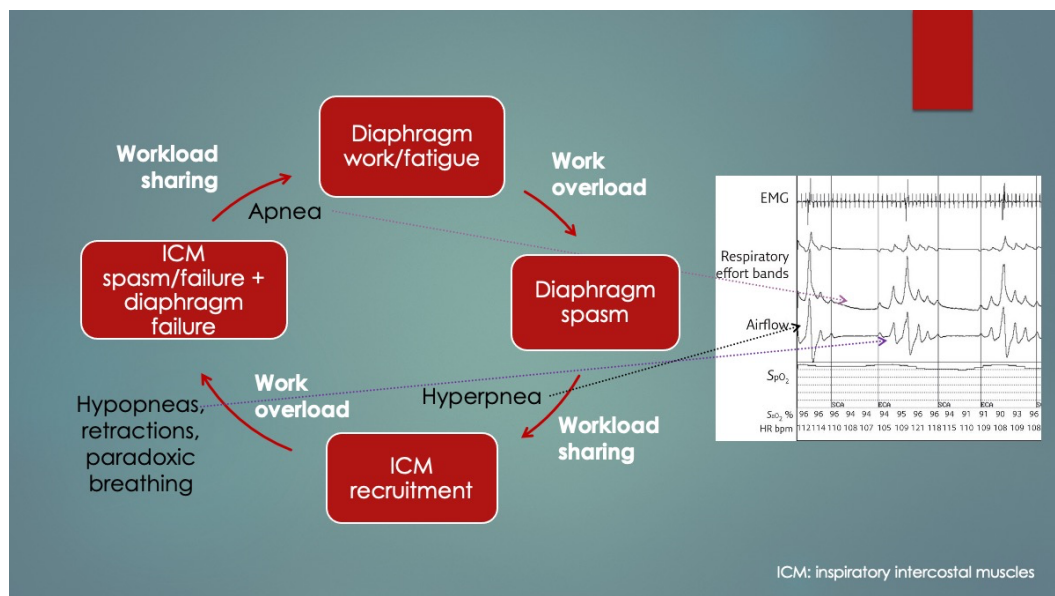
Figure 7 – Periodic breathing is hereby proposed to involve cyclical diaphragm fatigue and spasms alternating with intercostal muscle fatigue and spasms. Due to respiratory load compensation, ventilatory workload shifts from diaphragm to ICM and back as each muscle group fatigues, fails by spasm and then recovers. Cyclical spikes in D-EMG, thought here to be diaphragm spasms, occur in association with hyperpneic breaths followed by hypopneas and transient apneas. Hypopneas are thought to occur from independent ICM action whereas apneas by simultaneous failure of both diaphragm and ICM. *Insert*: Periodic breathing in an infant. Courtesy of Dr Sadasivam Suresh, Dept of Paediatric Respiratory and Sleep Medicine, Queensland Children's Hospital, Brisbane, Australia. *Insert source*: Urquhart DS, Tan HL. Sleep disordered breathing at the extremes of age: infancy. *Breathe* (Sheff). 2016.

Diaphragm Fatigue, Excitation and Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) in children and adults is a highly prevalent, frequently underdiagnosed condition. Sleep disorders are often missed by parents or the individual. OSA too carries significant short and long-term morbidity and mortality. Complications include systemic and pulmonary hypertension, cardiomyopathies, congestive heart failure, coronary artery disease, cardiac arrhythmias, stroke, venous thromboembolism and increased risk for SCD [61]. It is also associated with gastroesophageal reflux which improves significantly with CPAP, however, the mechanism linking the two has remained unknown [62]. Like HE above, but in older children and adults with OSA, transient diaphragm spasms and compensatory RAM action are hereby proposed to cause the observed apneas and hypopneas, respectively, as seen in **Figure 8**. This is not to dismiss the existence of upper airway (supraglottic) obstructions from atonic muscles or enlarged tonsils. In fact, they contribute to DD because of the increased work of breathing from added airway resistance. Furthermore, this novel diaphragmatic paradigm of OSA states that obstruction develops when RAM independently attempt to breathe against the immobilized diaphragm inactivated by spasm. This would explain the doubling of pulmonary resistance mentioned above which was associated with HE in mechanically ventilated infants [43]. It is also supported by *Southall's* anecdotal findings of initial resistance to inflating the lungs when resuscitating those with severe HE, even with functioning tracheostomy or endotracheal tubes in situ (maintaining airway patency) [31].

Additional support comes from *Miller et al* (1993) [63] who revealed in the breaths immediately preceding and following apneas in preterm infants, there was a stepwise increase in total pulmonary airway resistance not caused by supraglottic muscle collapse. Other evidence linking diaphragm involvement in OSA comes from an EMG study comparing activation of the respiratory muscles, including those of the upper airway, ICM and diaphragm in adults with OSA, with healthy controls [64]. All such respiratory muscles in the test subjects were more active than controls, both awake and asleep, reflecting an added workload. Moreover, with the onset of airway obstruction, there was a breath-to-breath, rapid drop in D-EMG followed by a gradual, then sudden increase with resumption of airflow a few seconds later. This was mirrored by similar changes in transdiaphragmatic pressures. The reduction was thought to be from reduced neural drive and an inhibitory reflex but could rather have been from diaphragm fatigue and spasm. It appears once the diaphragm had recovered from spasm it was able to resume functioning, however, a higher level of work was needed initially, probably to overcome airway resistance by diaphragm hypercontraction and immobility as well as the resistive elastic forces of pulmonary compliance.

It follows then from chest impedance studies in OSA, that when RAM function independently of a diaphragm inactivated by spasm, low amplitude hypopnea waveforms are produced. These would mimic obstructive apneas (**Figure 8B**) and, at bedside, might appear with rib retractions and paradoxic breathing (thoraco-abdominal asynchrony). By contrast, when both diaphragm and RAM are simultaneously inactivated (like in respiratory flutter but rather by "co-spasms"), near-flatline apneas appear, mimicking central apneas (**Figures 8A & C**). Once spasms finally resolve, ventilations would resume (but initially at higher intensity). Indeed, upon careful scrutiny of impedance, flow and D-EMG waveforms in central apneas, most often seen is a fine, tremulous baseline. This could represent highly attenuated diaphragm electrical activity by spasm. In fact, many central apneas in one D-EMG study were determined to be from another cause [65].
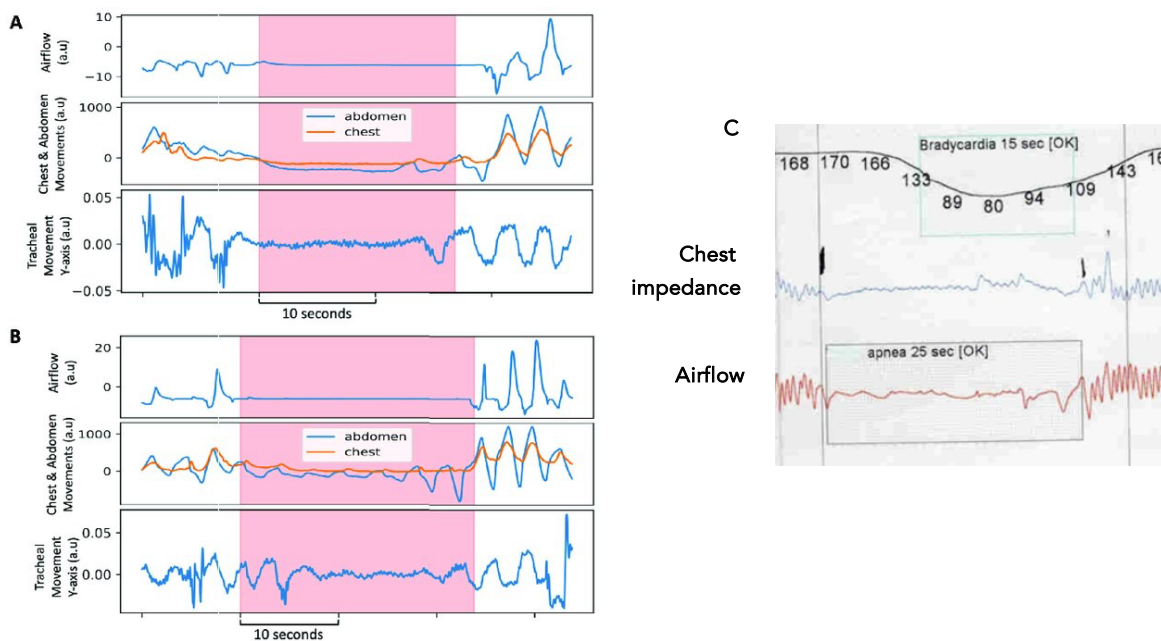
Figure 8 (A-C) – Central versus obstructive sleep apneas measured by airflow and impedance plethysmography. Central and obstructive apneas (pink shading) may in fact have peripheral (diaphragmatic) origins (A) Central apneas exhibit no airflow and lack of respiratory movements of chest and abdomen. They are presumed to occur by lack of neural stimulation to the ventilatory muscles but could rather be from combined primary diaphragmatic failure with inactive RAM. (B) Obstructive apneas involve no airflow associated with respiratory movements, here seen as reduced-amplitude hypopneas (middle frame). Supraglottic muscle collapse is thought responsible but could rather be isolated RAM activity breathing against an immobile diaphragm. (C) "Central" apnea with flutter-like or fibrillatory chest movements (blue line) with brady-hypopneas (red). Although cardiac artifacts could be responsible, so could respiratory flutter.
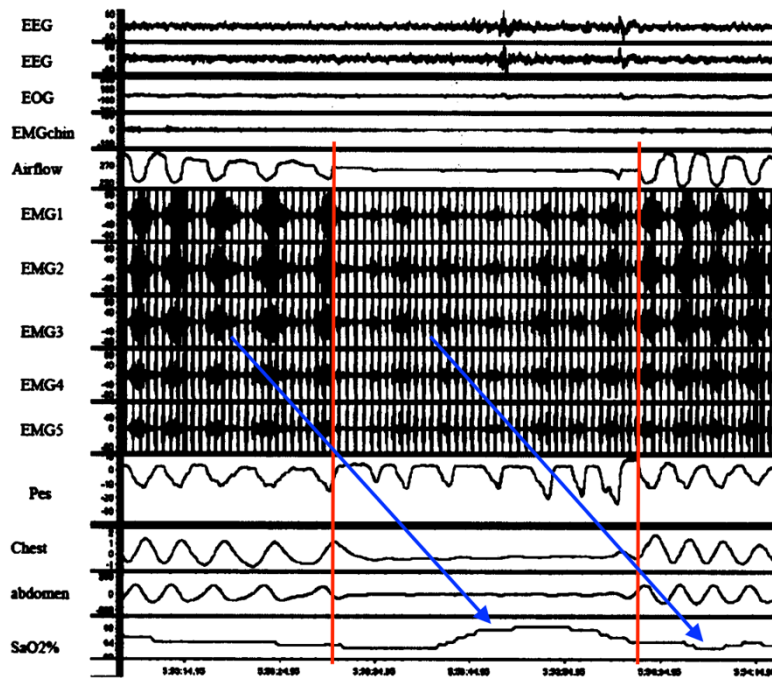
Figure 9 – Evidence for diaphragm electromechanical dissociation in a sleep apnea (esophageal D-EMG1-5). Blue arrows show the delay in oxygen desaturations after a pathological event involving the diaphragm that exhibited periodicity. The apneic period occurs between the two red lines where there was no airflow or respiratory movements (seen in RIP chest and abdomen). This would therefore be classified as a central apnea. However, there was D-EMG neural activity (albeit attenuated), thus, it is not central. Obstructive sleep apnea would then be presumed, however, that normally involves continued breathing movements, of which there were none. Instead, something else was impairing ventilations associated with reduced D-EMG (i.e., diaphragm spasm). Continued P_{es} activity during the apnea could have been caused by independent action of the accessory muscles, while the attenuated D-EMG from continued neural input during the spasm. It appears a complete novel airway obstruction developed by RAM attempting to inspire against the temporarily inactivated, immobilized diaphragm. Airflow resumed, but with increased D-EMG activity, presumably to overcome airway resistance. *Reproduced with permission.* Source: Luo YM, et al. Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. *Chest*. 2009. [65]

Figure 9 is very important because it temporally connects abnormal diaphragmatic electrical activity on intra-esophageal D-EMG in an adult apnea with a complete lack of ventilatory movements. It was neither a classic central, obstructive nor even mixed apnea. Although cause and effect cannot be ascertained, there was significant attenuation of D-EMG amplitude (and frequency) during the episode. Combined with the lack of respiratory movements, this is consistent with diaphragm inactivation due to spasm (electromechanical dissociation). Respirations resumed but only with higher intensity electrical bursts (perhaps from increased neural drive and higher diaphragm work to overcome post-obstruction airway resistance). Also, although truncated, D-EMG and oxygen saturations exhibited periodicity, suggestive of respiratory load cycling with RAM. Lastly, this evidence suggests that normal D-EMG activity reflects not just neural drive, but rather a composite influenced by diaphragm electromechanical output.

A final (and rare) piece of evidence linking diaphragm hyperexcitation with abnormal breathing was found in a case report of three tetraplegic patients with generalized body

spasms triggered by deep breaths or sudden body movements (both increase ventilatory workload) [66]. Using esophageal D-EMG, **Figure 10** demonstrates the electrical waveform of a diaphragm spasm with a prolonged apnea. Apnea duration was longer than the spasm, supporting the notion of continued diaphragm inactivity by delayed relaxation (or resetting). Interestingly, symptoms occurred more often in colder environments and if anxiety was present (the former a SIDS risk factor while the latter a known trigger of DHD and HE).
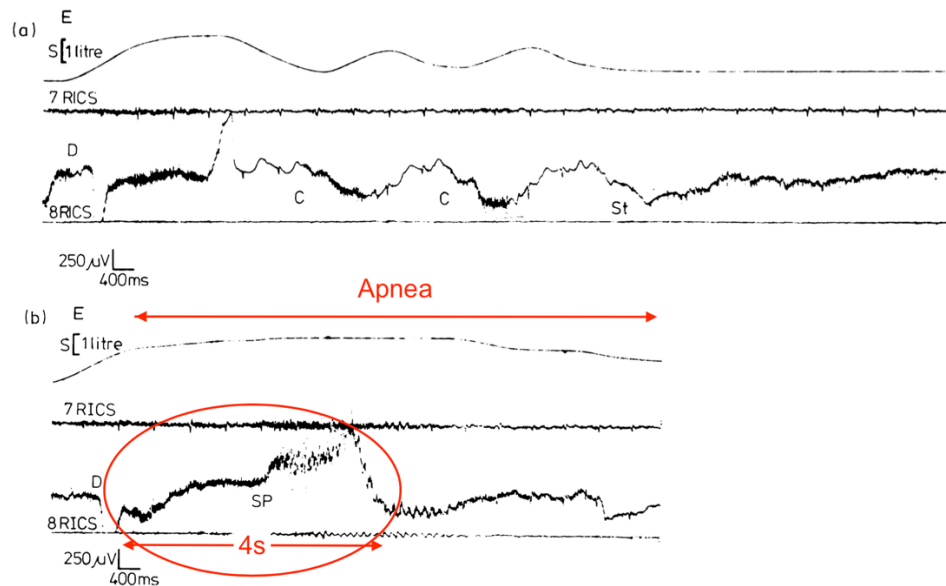
Figure 10 – Spirometry (top, "S"), intercostal EMG ("7,8 RICS") and diaphragm EMG ("D") during a generalized spasm in a tetraplegic adult with dyspnea. Continuous tracing from (a) to (b). Breathing stopped in association with coughing (C), straining (St) and a diaphragmatic spasm (SP; red ellipse). This would otherwise have been deemed a central apnea. It persisted longer than the spasm, presumably due to delayed recovery of diaphragm function. With permission by BMJ Publishing Group Ltd license (August 2024) [66].

Nocturnal sweating is another known SIDS risk factor and hypothesized here to be secondary to overheating from increased diaphragm work, exacerbated by fevers and overwrapping in bed. In an Icelandic study of adults with OSA, frequent night sweats (≥3 times/week) were reported by 30.6% of male and 33.3% of female patients compared with 9.3% of men and 12.4% of women in the general population (p<0.001) [67]. Boys are also more likely to have night sweats than girls [68], potentially reflecting increased work of breathing. Evidence to support harder working, fatigue-prone respiratory muscles in boys compared to girls include: (1) significantly thinner diaphragms on ultrasound in preterm [69] and adult males [70], (2) a faster rate of diaphragm fatigue along with lower inspiratory endurance times based on transdiaphragmatic pressures in adult males [71] and (3) higher

overall respiratory morbidity and mortality in preterm males [72]. Additionally, adult females demonstrated greater recruitment of ICM compared to males due to anatomic rib differences, thus reducing diaphragmatic workload [73]. Lastly, male neonate mice exposed to in utero asphyxia for 7.5 min had decreased survival at one hour after birth compared to females (survival rates 52% and 69%, respectively) [74]. Their diaphragms demonstrated significantly worse structural and functional deficits (reduced maximum tetanic force and fatigue resistance), persisting long-term in those that survived, but associated with higher morbidity and mortality. All these findings provide a compelling explanation for the male preponderance of SIDS cases.

Another important point about night sweats is the potential perils of polar fleece and other synthetic fabrics commonly used for bedding and clothing in children. Essentially, these do not breathe (ventilate heat) or wick body moisture like natural fabrics do [75]. Overheating might result, leading to increased risk of SIDS and SUDC, especially when febrile. This could reduce the DCC threshold by worsening fatigue.

Peripheral Respiratory Failure in Septic and Cardiogenic Shock

Diaphragm muscle fatigue and failure have been reported in septic Mongrel dogs. In ten spontaneously breathing anesthetized animals given intravenous *E. Coli* endotoxin, all died within 4.5 hours by respiratory arrest. *Hussain et al* (1985) [39] determined by transdiaphragmatic pressures and EMG of diaphragm and ICM, that all cardiac arrests in severe sepsis were preceded by rapidly progressive diaphragm fatigue and sudden failure. This refuted traditional thought, that CNS depression coupled with severe lung disease was the cause of alveolar hypoventilation, severe hypoxemia and death. Unfortunately, such techniques could not reveal if diaphragm excitation had occurred. However, the authors mentioned how diaphragmatic failure was not unique to sepsis as it had also occurred in animals with cardiogenic shock induced by cardiac tamponade. That was in reference to *Aubier et al* (1981) [76] who had injected saline into the pericardial cavities of 13 spontaneously breathing adult dogs compared to seven on MV. Like severe sepsis, deaths occurred quickly, within 2.5 hours, in all those of the former group secondary to progressive diaphragm fatigue and sudden failure. Electromechanical dissociation had occurred whereby neural drive was maintained to the diaphragm (as measured by phrenic nerve root electrodes) but the respiratory muscles failed as force generators. Three possible causes were outlined: (1) blockage of nerve impulses at the neuromuscular junction, (2) impairment of excitation-contraction coupling and/or (3) failure of the contractile machinery itself. The latter was reasoned most likely, in keeping with putative DCC, and probably had occurred

from the effects of diaphragmatic hypoperfusion in shock. This would have led to local hypoxemia and a shift to anerobic metabolism within the diaphragm, along with lactic acid accumulation contributing to the contractile dysfunction and organ failure. By extension, under high respiratory rates, when there is less time for diaphragm perfusion to occur, local hypoxia and acidosis would be exacerbated [77]. This fatigue-failure process in hypoperfusion is supported by a study in which diaphragm perfusion pressures were directly increased via phrenic artery catheters after diaphragm fatigue was induced in anesthetized, ventilated dogs [78]. It reversed the DD.

A pattern emerges from the above two circulatory shock experiments (septic and cardiogenic), wherein respiratory fatigue and rapid failure preceded cardiac arrests in previously healthy, spontaneously breathing animals. Hypotension with reduced diaphragmatic perfusion appears to be the common pathologic mechanism wherein blood supply did not meet the metabolic demands of the organ. Anemia (already discussed) and hemorrhagic shock [79] would worsen this as well as deficiencies of oxygen and substrates like glucose, fatty acids and electrolytes such as potassium, calcium, phosphorous and magnesium, which are important in excitation-contraction coupling. Indeed, acute hypophosphatemia has been linked to respiratory fatigue in hospitalized patients [80] and associated with prolonged MV and delayed discharge from the pediatric ICU [81]. More than one author has suggested this in SIDS causation where hypomagnesemia too has been suspected in causing severe *limb* muscle weakness worsened by prone position (asphyxia hypothesized from inability turning head to avoid rebreathing) [82]. However, we now have a stronger mechanism that links all such electrolyte and metabolic abnormalities, and it centers on sudden diaphragmatic failure.

As such, in a young infant sleeping at home with dehydration, acute electrolyte disorders and acidosis from both metabolic and respiratory causes as well as perhaps diaphragm viral myositis (*vide infra*) — all compounding hypoxemia and hypercapnia worsened by diaphragm fatigue — it could be as simple as an acute workload increase by REM-sleep or a roll to the prone position that suddenly triggers excitation by DCC. Acute bilateral diaphragmatic paralysis and respiratory failure would ensue, followed by RAM activation (if arousal occurs) and terminal struggle to breathe against the internal airway obstruction produced by the hypercontracted diaphragm. Within only 1-2 minutes, critical hypoxemia, bradycardia, cardiac arrest and death would occur. All the while happening silently and without warning, unwitnessed and with rapid deterioration ultimately leading to a postmortem SIDS diagnosis. **Table 3** describes such a sequence of diaphragm fatigue-DCC-respiratory arrest in a hypothetical infant sleeping *upstairs* in a smoking household in a cold winter climate with artificial home heating.

1	Gradually progressive DD, hypoxemia and hypercapnia occur by cumulative effects of prone sleeping (rebreathing, higher diaphragm workload) as well as viral URI diaphragm myopathy and nicotine absorption from cigarette *smoke* (in an *upstairs* bedroom of a *heated* household).
2	Fluid losses from fever, decreased oral intake, sweating and bicarbonate-rich diarrhea over past 24 hours. Along with overheating and further rebreathing from loose, heavy bed blankets; sweating, dehydration and hyperthermia develop, adding workload. Further hypoxemia, hypercapnia and metabolic and respiratory acidosis ensue, all exacerbating DD.
3	Compensatory RAM recruitment while awake (respiratory load sharing). Inspiratory intercostal muscles activated. Observed bedside as rib retractions.
4	Like fatigued limb muscles exposed to higher workloads, diaphragm hypertonicity and neuromuscular excitation develop.
5	Infant falls asleep. REM-sleep inactivation of RAM by CNS. Sudden workload placed on fatigued diaphragm putting it above cramp threshold. Precipitates painful bearhug of DCC that paralyzes the diaphragm, immediately inducing critical diaphragm failure.
6	Oxygen saturations slowly begin to drop at first yet insufficient to trigger alarm.
7	Infant arouses from the painful cramp (or critical hypoxemia) but with silent, ineffective gasping and apnea from DCC. Unable to cry out because of inspiratory arrest. RAM reactivated with waking.
8	Independent of diaphragm, RAM contract to expand ribcage and lungs to inspire. Met with combined resistance of pulmonary compliance and the hypercontracted, immobilized diaphragm. Like attempting to inspire against a 100% upper airway obstruction, the agonal breathing creates negative intrathoracic pressures (yet insufficient to expand lungs).
9	No apnea alarm because chest movements continue with inspiratory efforts.
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 exposed to the negative pressures (Tardieu spots). This is potentially exacerbated by effective clamping of inferior vena cava and aorta at their hiatuses by the hypercontracted diaphragm.
11	Infant loses consciousness from hypoxemia. RAM weaken.
12	Hypoxia, bradycardia and/or lack of respiratory 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 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-contracture, DD: diaphragm dysfunction (fatigue), RAM: respiratory accessory muscles, REM: rapid-eye-movement sleep, URI: upper respiratory infection

Table 3 – Sequence of at-home respiratory arrest by DCC in an infant. This is a hypothetical example of an otherwise healthy 3-month-old with low-grade fevers, rhinorrhea, congestion, cough and loose stools from a typical viral infection over the past 24 hours. He is sleeping alone in a crib upstairs in a smoking, heated household in winter. Heart rate, oxygen saturations and respiratory movements (but not airflow) are being wirelessly monitored using a typical home SIDS device. Progressive diaphragm fatigue terminating in pathological excitation by DCC with resultant novel airway obstruction is central to this SIDS hypothesis.

Diaphragm & Limb Myopathy, Contraction Band Necrosis and Tardieu Spots

It is proposed that respiratory arrest by DCC is responsible for some SIDS and SUDC cases as well as some SCD in adults. Like the novel obstruction of OSA outlined above, where diaphragm spasm mechanically resists RAM contractions (causing *transient* apneas-hypopneas), *sustained* apneas would occur in DCC. If not overcome by autoresuscitation or rescue breaths, asphyxia and death ensue. Unfortunately, like ventricular fibrillation, pathological pump contractions are temporary and do not persist postmortem, making it impossible to confirm at autopsy. However, *Kariks* (1989) [83] found indirect evidence in the diaphragms of SIDS victims. Although controls were not provided, contraction band necrosis was present in 82% of diaphragms (D-CBN) along with focal-to-diffuse myofiber ruptures (sarcomere disruptions) and fibrous scars. Acute inflammatory cell infiltrates were not seen (suggesting a hyperacute process). Tissue staining revealed that some sort of diaphragmatic *hypercontraction injury* (causing irreversible sarcomeric spasm) had occurred terminally and acutely under prolonged anoxia, leading to contracted segments of thick and thin muscle filaments. Fibrous scars in various stages of healing suggested prior non-fatal injuries had occurred by repeated HE in the preceding days to weeks. *Silver & Smith* (1992) [84] confirmed these myopathic findings, stating D-CBN was common in 125 neonates and infants that had died suddenly, primarily by asphyxia. This included birth asphyxia, drownings, suffocation, severe burns with carbon monoxide poisoning and SIDS. Other modes of death included meningitis, head injuries and acute dehydration from severe gastroenteritis [85]. They remarked, "The morphologic age and, if present, stage of healing in each case suggested that the diaphragmatic lesion commenced at or shortly before death or at the time of the cardiac arrest that led to death". Despite such compelling results, and a few other reports, research in this promising area stalled. Regardless, the evidence makes it imperative to **start including diaphragm histology in all autopsies involving sudden unexpected deaths**.

A clue to the origin of the diaphragm myopathy in SIDS comes from a study involving acute loading of rabbit inspiratory muscles, well above their fatigue thresholds [86]. In other words, extreme exercise. Along with significant hypercapnia and respiratory acidosis (both suggesting diaphragm insufficiency), post-euthanasia sarcomere disruptions with significantly inflamed and necrotic diaphragm tissues were demonstrated in all test animals. Moreover, this occurred in a load-dependent manner (i.e., higher ventilatory workloads correlated to larger areas of myopathy). There was no mention of D-CBN, however, none of the rabbits had died during testing (i.e., presumably no DCC). Interestingly, only 1% of the diaphragm surface area fraction was abnormal, occurring most often in the costal diaphragm and less so in the crural portion and parasternal intercostals. Injured fibers were

more widespread throughout the diaphragm in some animals, whereas localized in others. Similar findings were disclosed in 18 preoperative COPD patients exposed to short inspiratory overloads compared to 11 preoperative controls with normal pulmonary function [87]. Intraoperative diaphragm biopsies revealed sarcomere disruptions in all, and significantly pronounced in the case patients (higher area fractions and densities). Necrosis and inflammatory cells were not observed, possibly due to shorter duration, less intense resistive loading.

In summary, excessive ventilatory workloads exerted load-dependent myopathic changes in the inspiratory muscles of test animals and humans similar to those identified in SIDS. Although little more was found in the literature on the mechanism of D-CBN — and despite no comparative evidence demonstrating muscle cramps as a cause of sarcomere disruption, inflammation or contraction bands in the limbs — progressive diaphragm fatigue culminating in critical excitation is a legitimate CBN candidate. In other words, DCC could be the hypercontraction injury seen in SIDS (and other sudden unexpected deaths). Simultaneous viral infections appear to contribute to the myopathy.

Similar histopathologic changes were reported in children with incapacitating leg cramps associated with viral influenza, predominantly serotype B. Conducted by retrospective analyses of hospital cases of influenza-associated myositis (IAM) as well as case reports and reviews articles, *Agyeman et al* (2004) [88] found that calf muscles alone or together *with other limb muscle groups* (undisclosed types) were involved in 69% and 31% of a combined 316 cases, respectively. There was a gender ratio of 2:1, male-to-female in these school-aged children of median 8.5 years age (range 2.5-14). Serum creatine phosphokinase (CPK, or creatine kinase) levels were massively elevated along with lactic dehydrogenase and aspartate transaminase. (*Skeletal* muscle troponin-I is even more sensitive and specific [89].) Ten children (3%) developed severe rhabdomyolysis, 8 had acute renal failure, 2 required MV and another one died. The authors referenced other calf muscle biopsy reports in pediatric IAM, demonstrating patchy necrosis with scant inflammatory infiltration in 11 of 12 in one series, and 28 of 35 with muscle degeneration, necrosis and scant infiltrates in another. Because of the lack of infiltration, the authors used the term myopathy in lieu of myositis. All such findings are important because the diaphragm too could be vulnerable to "direct muscle invasion by virus particles or immune-mediated muscle damage". This could have been responsible for the two cases requiring MV and the one who died. Cell injury along with inflammatory mediators might have contributed to progressive diaphragm fatigue, excitation and ultimate respiratory failure. Indeed, *Eisenhut* (2011) [90] reported marked diaphragmatic abnormalities in a 5-month-old girl admitted with RSV bronchiolitis and poor feeding who succumbed in hospital to a

sudden unexpected death. Although grossly normal, diaphragm histology revealed myofiber destruction, focal segmental myocyte necrosis, myocyte regeneration and focal infiltrates of macrophages and small lymphocytes. Interestingly, similar findings were reported in COVID-19 deaths in adults [35]. Such changes provide even more support to evaluate diaphragm histology in sudden death cases involving viral (or bacterial) infection. Moving forward, serum CPK, CK-MM or sTnI levels and venous blood gases could screen for, and risk-stratify those at risk for respiratory decompensation by critical diaphragm fatigue and excitation.

H High CPK levels were also reported in malignant hyperthermia, where there is limb muscle rigidity, spasms, rhabdomyolysis and myonecrosis caused by various anesthetics. Like *Kariks'* SIDS diaphragms, limb histology revealed CBN, segmental necrosis and degenerating muscle fibers caused by "prolonged hypercontraction"[23]. Perhaps by extension then, some of the deaths in this high mortality condition are caused by respiratory myopathy and Type II failure by DCC. Although no autopsy reports were available examining diaphragm histology in malignant hyperthermia, preceding DD is supported by the author's mention of "unexplained persistent rises in end-tidal CO_2 levels".

Another important finding at autopsy in SIDS and SUDC are intrathoracic Tardieu spots. These are petechial hemorrhages found on the linings of thoracic organs exposed to terminally negative air pressures, such as the epicardium, pleurae and intrathoracic thymus (**Figure 11**) [91]. They are present in roughly 80% of SIDS [92] and 50% of SUDC [93] (as well as 30% SUDEP [94]),also seen in septicemia, barotrauma, heat stroke, severe burn injuries and some electrocutions [95]. Like the *Poets* study [3], they are thought to occur by agonal breathing against airway obstruction (terminal ineffective gasping). Again, the cause has never been elucidated, only speculated to be laryngospasm or bronchospasm. The novel airway obstruction of DCC, however, could be it. This also provides a uniting terminal mechanism among the various causes of Tardieu petechiae.
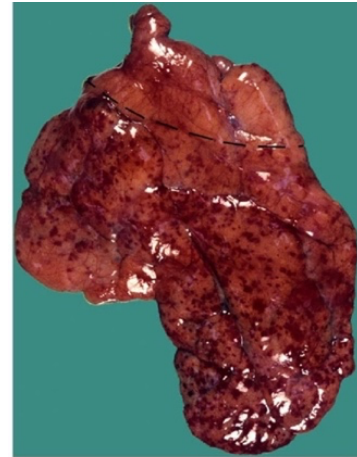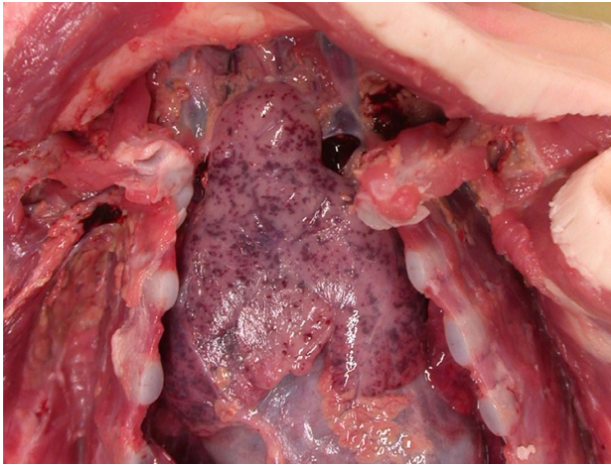
Figure 11 – Tardieu petechiae.
Left: Fetal thymus covered with petechiae. Right: Infant thymus showing distinct boundary between the intra- and extrathoracic portions, with and without hemorrhages, respectively (broken line). With permission: © Prof. Paul N. Goldwater (left), © Prof. Roger W. Byard (right)

Beckwith's 1988 paper on Tardieu spots provides an excellent account on their pathogenesis [96]. Two things require mention: (1) vigorous respiratory efforts are required to produce them, and (2) they developed when airway obstruction was induced experimentally at *end-expiration* and not any other phase of respiratory cycle. Again, this is consistent with the case patient's observation of bearhug apnea always being triggered at end-expiration. Perhaps maximal negative intrathoracic pressures are generated then, when DCC obstruction strikes, and tidal volume is fully expelled thus giving a mechanical advantage to produce the hemorrhages. Moreover, it is just after this phase of the respiratory cycle when diaphragm contractions are first initiated (by neural stimulation). Like limb muscles, this is precisely when cramps are initiated — that is, upon their initial shortening [97]. Future studies to reproduce Tardieu spots might be accomplished by inducing bilateral diaphragmatic paralysis in anesthetized infant test animals by bilateral surgical phrenectomies.

A fascinating response arises as to the question of why the case patient first experienced DCC at age 7 and not any sooner. The only thing that had changed in his young life was ceasing his lifelong history of nocturnal thumb-sucking. Surprisingly, literature review revealed several papers, including systematic reviews, supporting the role of pacifiers (dummies) as being SIDS-preventative [98]. Perhaps they reduce diaphragmatic workload or minimize ventilatory pausing at end-expiration (when the diaphragm relaxes maximally and about to contract for the next cycle), thus negating the opportunity for DCC to strike. Unfortunately, studies comparing respiratory waveforms both with- and without

pacifiers could not be found. This too should be studied, though, perhaps best accomplished by chest impedance, RIP, EMG and airflow monitoring using sleeping infants as their own controls.

Moving forward, experimentally confirming and reproducing all above pathological findings might be best accomplished by delivering percutaneous electrical currents to the diaphragms of anesthetized test animals. Even better, rebreathing nicotine and exhaled gases in dehydrated, septic, hyperthermic and acidemic animals might accomplish it. In addition, it would be helpful to look for such changes in nicotine overdose deaths. This is important not only because of its extreme potency but also the ubiquity of nicotine vaporizer solutions worldwide and thus, cumulatively massive potential for serious harm by unintentional oral overdose, especially in children as they are most vulnerable. Treatment in such cases could start with preventing hyperexcitation by reducing DD and workload.

Potential Complications of DCC — Speculation Alert!

A host of serious pathological consequences might stem from the unique combination of diaphragm anatomy, hypertonicity and pathological excitation. Nowhere else does this appear in the body. Looking at **Figure 12**, the musculotendinous diaphragm wraps around three tightly enveloped hiatuses, each providing passage of an important structure: the inferior vena cava (IVC), aorta and esophagus.
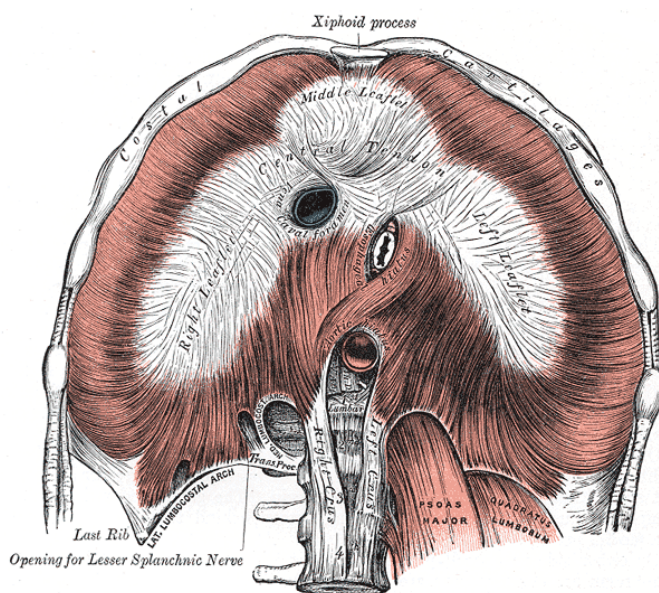
Figure 12 – Anatomy of the inferior (abdominal) diaphragm. The diaphragm is composed of tendon and muscle which tightly wrap around three apertures (hiatuses): the inferior vena cava (IVC), aorta and esophagus. Diaphragm excitation could effectively clamp these structures leading to potentially serious hemodynamic and gastrointestinal consequences both above and below the diaphragm. *Courtesy of Henry Vandyke Carter. Public domain,* [*Wikimedia Commons*](#)*, 2008.*

Under increased diaphragmatic tone, spasms, cramps and other DHD, these structures could become squeezed and effectively clamped by the diaphragm itself. Duration and intensity would dictate symptoms, also depending on the degree of hypertonicity and form of excitation: from transient in spasms, to rhythmic in flutter and sustained in hypertonia and cramp-contracture. Increased tonic electrical activity of the diaphragm (Edi) in PICU patients was associated with the sickest ones in the acute phases of illness, with Edi higher in those with bronchiolitis, tachypnea and hypoxemia [99]. Occurring most often in spontaneously breathing patients and affecting the youngest patients (0-12 months), hypertonic Edi even predicted extubation failure. Support for esophageal clamping is already provided by those with diaphragm flutter who had a variety of gastrointestinal complaints including hiccups, belching, retching, acid reflux, vomiting and epigastric (or chest) pain [100]. Similarly, reflux occurs in OSA as mentioned above, and improves with CPAP [62]. It could be caused by intermittent esophageal clamping and release from diaphragm spasms combined with negative intrathoracic pressures generated by breathing against the diaphragm. The reduced diaphragmatic workload of CPAP would explain the improvement. Alternatively, GERD in OSA could be secondary to esophageal sphincter weakness or increased gastric acid secretion with decreased salivation and swallowing during sleep. However, none of these would be expected to improve with CPAP whereas diaphragm spasms would. Notably, a medical history of reflux-aspiration is also common in sudden infant deaths [2], supporting the notion of diaphragm hyperexcitation. Also, it is interesting to consider that acute anxiety might physically manifest at the diaphragm. It too could increase tone, leading to the commonly experienced gastrointestinal complaints that are near-identical to those of diaphragm flutter. But what follows next is even more speculation on a host of potential complications from a hemodynamic-cardiopulmonary standpoint.

As opposed to the aorta, the IVC is thin-walled and under lower vascular pressures, thus more collapsible by clamping. Cardiac preload would drop, leading to reduced stroke volume and cardiac output. Along with aortic clamping and negative intrathoracic air pressure from breathing against obstruction, pulmonary arterial hypertension (PH) and raised hydrostatic pressures in the lungs would develop resulting in pulmonary congestion and edema. With transient diaphragm spasms these changes would be reversible, and the patient likely survives (consistent with a diagnosis of noncardiogenic pulmonary edema if substantial). However, with persistent clamping by DCC combined with agonal breathing, the PH and such findings would worsen (also forming Tardieu petechiae). Other associated pathologies from aortic clamping could include simultaneous acute left- and right-sided dilated cardiomyopathies (possibly Takotsubo cardiomyopathy), labile hypertension with

hypertensive urgency/emergency and acute heart failure with increased risk of arrhythmias and sudden deaths. Severe hypotension (shock) inferior to the diaphragm would lead to diaphragmatic hypoperfusion leading to further hypoxemia and diaphragm excitation. This might explain the drastic desaturations observed in neonates with HE. It could also explain the increased risk of necrotizing enterocolitis seen in preterm infants [43]. Right-to-left cardiac shunting is possible too, perhaps through a patent foramen ovale or ductus arteriosus. This could explain paradoxic motion of the interventricular septum [101] and valvulopathies seen in OSA [102]. With IVC clamping, hemostasis of the venous circulation below the diaphragm would occur, thereby contributing to venous thrombosis of the lower extremities with raised risk of thromboembolism (VTE) as well as pulmonary embolism and even stroke (paradoxical embolus through patent foramen ovale). Indeed, OSA has been identified as an independent risk factor for VTE (and stroke) [103]. In that paper, the proposed mechanisms (i.e., pro-inflammatory state, intermittent hypoxia and endothelial dysfunction) do not weigh up to the major mechanical, hemodynamic changes of DHD proposed here.

Lastly, persistent esophageal clamping by agonal DCC would keep stomach contents held under pressure, only to be suddenly released and expelled postmortem from diaphragm relaxation. These would collect in the mouth and airways, commonly seen at autopsy in SIDS and other sudden unexpected deaths (e.g., SUDC, SUDEP, malignant hyperthermia) [104]. Alternatively, these findings could be artifacts due to passive movements from postmortem body handling (CPR was ruled out in an autopsy study [105]).

Evidence supporting the above co-pathologies in DHD was scarce; however, some was provided by elevated pulmonary arterial pressures, as measured by echocardiography and right heart catheterization (gold standard). Transient PH was demonstrated in preterm infants with the onset of HE [31]. It was also implicated in OSA in adults (particularly during REM-sleep) [106], SUDEP sheep models [107] and most recently, Type II respiratory failure in an adult with congenital myopathy [108]. In all such cases, PH was idiopathic. Autopsy evidence supporting putative DCC clamping of the IVC in SUDC included a report of brain weights exceeding the 100th percentile in 53 of 56 cases, associated with cerebral edema and vascular congestion [93].
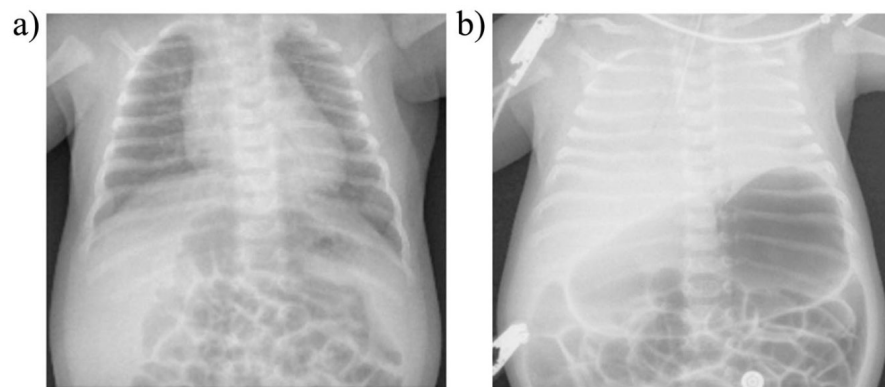
Diaphragm Failure in Bronchiolitis Deaths

Deaths in children with bronchiolitis, primarily from RSV, generally occur either by gradually increased work of breathing causing sudden ventilatory muscle fatigue and failure or by sudden respiratory arrests [109, 110]. In either case, death occurs by terminal apnea.

It shares risk factors with SIDS and SUDC, affecting younger or premature infants and those with preexisting chronic respiratory, cardiac and neuromuscular diseases as well as having a sudden, rapid and unpredictable onset. Healthy infants can be affected too, in which apneas strike without preceding signs of infection or respiratory distress. The bronchiolitis occurs from lower respiratory infection by community-acquired viral infections that typically are not fatal. However, infiltrates and atelectasis add diaphragmatic workload, where, along with other fatiguing factors similar to above in illness, are proposed to trigger DCC apnea from a sudden ventilatory workload surge. Alternatively, the terminal apnea could be centrally caused: by direct CNS viral infection with resultant cerebral inflammation and edema impairing the respiratory centers [111].

Figure 13 reveals significant abnormalities on chest X-ray that rapidly developed in a 40-day-old infant admitted with RSV. The baby, who had presented with fever, cough and wheezing, suddenly deteriorated with respiratory distress marked by hypoxemia, hypercapnia and respiratory acidosis. Terminal apnea and death occurred before intubation could be done. Complete opacification of both lung fields with an air-dilated stomach and proximal bowels developed in less than two hours (not from misguided intubation). No explanation was provided. Although diaphragm pathology was not reported, the clinical findings and X-ray changes were consistent with progressive diaphragm fatigue (insufficiency), sudden failure (respiratory arrest) and agonal airway obstruction by DCC. Terminal obstructive RAM efforts could have led to substantially negative intrathoracic pressures with resultant pulmonary circulatory shunting, edema, hemorrhage and fluid extravasation. Also, intrapulmonary air could have been forced into the digestive tract, perhaps trapped by the putative esophageal hiatus clamp, leading to reduced pulmonary expansion from increased intra-abdominal pressure. By contrast in intubated MV patients, such findings have not been reported to our knowledge. This could be due to a reduced work of breathing preventing DCC.

a)   b)

Diaphragm Failure in Seizure Deaths (SUDEP)

There are several overlapping historical and autopsy findings in SIDS, SUDC and SUDEP, and this suggests a common pathological mechanism. We believe this to be DCC. SUDEP typically affects young adults who suddenly expire silently, unwitnessed at night, probably while sleeping, only to be found afterwards without overt signs of distress in prone bed position with aspirated gastric contents in mouth and airways. The lungs are very "wet" and heavy, engorged with blood and fluid. Tardieu spots are not uncommon (at least 30% of cases). These findings are in keeping with those of *Zhang et al* (2022) [94] who, using controls, determined at autopsy the primary mechanism of death in 13 SUDEP cases was *asphyxiation* (Tardieu spots, pulmonary congestion and hemorrhages). Those in prone position were at significantly higher risk. Generally, other than this, autopsies in SUDEP are considered "negative", but yet again, diaphragm histology is not being done.

Zhang's findings are supported by *Ryvlin's* MORTEMUS study (2013) [112], which elucidated terminal events in fatal seizures by retrospectively assessing patients who had continuous EEG, video and basic cardiorespiratory observations (respiratory *movements*) performed and recorded at epilepsy monitoring units. In ten confirmed SUDEP cases, postictal tachypnea occurred in all followed by *terminal apnea* and cardiac arrest either within three minutes or delayed by 11 min after temporary restoration of cardiorespiratory function. Over 90% had died in the prone position. This redirected attention from the heart to respiratory system and CNS in SUDEP. Most of the seizures had started in the temporal lobe, a region involved in volitional breathing. Although the precise cause could not be elucidated (no airflow, chest impedance, oxygen saturations or end-tidal carbon dioxide levels), the terminal apnea was speculated to be *centrally mediated* from "post-generalized EEG suppression". However, this is at odds with the asphyxia of the *Zhang* study and its autopsy findings. Instead, periictal diaphragm excitation and consequent fatigue could have occurred by seizure transmission along the phrenic nerves. Seizure spread to a peripheral nerve (recurrent laryngeal), causing end-organ (laryngeal) spasm and respiratory arrest is not a unique idea, as it was performed experimentally in rats [113]. Intracellular and systemic lactate, a byproduct of seizure causing metabolic acidosis, could have developed and worsened postictally, thereby contributing to progressive lengthening of diaphragmatic T_R, worsened by postictal (compensatory) tachypnea. This would take time

to develop and is consistent with the delayed-onset deaths. <u>Postictal diaphragm fatigue worsened by prone positioning, REM-sleep, progressive hypoxemia, critical acidosis and hyperacute electrolyte disorders could have ultimately culminated in the terminal apnea by DCC</u>. Given the silent, internal struggle of DCC obstruction, this would not have easily been picked up by the cardiorespiratory observers. The general scheme for DCC in SUDEP is depicted in **Figure 14.**
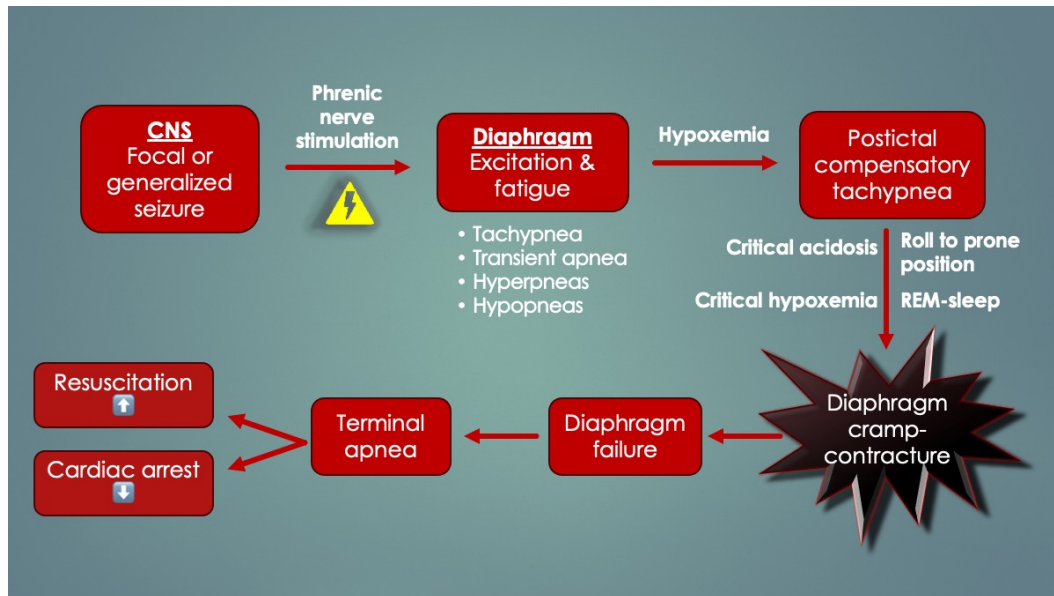
Figure 14 – Postictal diaphragm cramp-contracture hypothesis in seizure deaths. This differs from other SUDEP hypotheses by (1) seizure-induced diaphragm excitation (and fatigue) carried by the phrenic nerve(s), (2) worsened fatigue from postictal tachypnea and (3) sudden excitation by DCC leading to silent terminal apnea and cardiac arrest. Postictal critical acidosis, hypoxemia, prone positioning and/or REM-sleep onset could catalyze DCC.

It is important for the DCC hypothesis to explain the rarity of deaths from SUDEP compared to the overall number of nonfatal seizures. **Table 4** lists potential factors contributing to survival versus mortality in seizures from a hypothetical DCC standpoint. Important *fatality* factors by immediate or postictal DCC include (1) the seizure involves and hyperstimulates the respiratory muscles (may not be always the case in seizure), (2) *bilateral* diaphragm hyperstimulation is followed by bilateral excitation in DCC leading to complete bilateral diaphragm paralysis, (3) preexisting diaphragm fatigue is worsened by seizure (i.e., contributions by prone positioning, nicotine exposure or intercurrent infections with dehydration and diaphragm myositis) and (4) sudden postictal RAM inactivation by REM-sleep or excitation (RAM spasms or cramps). *Survival* factors include (1) subcritical seizure

duration (minimal postictal metabolic derangements like lactic acidosis and overheating), (2) subcritical hypoxemia (no cardiac arrest) and (3) postictal diaphragm spasms that are transient and recoverable but not persistent like DCC.

Mortality factors in seizure
Sz hyperstimulation of respiratory muscles (D ± RAM)
Sz hyperstimulation of bilateral D
Sz hyperstimulation of D is complete (all segments involved)
Critical preexisting diaphragm fatigue (male, prone, nicotine, dehydration, infections, myositis, pharyngeal OSA, pulmonary or neuromuscular diseases)
Ictal/postictal rebreathing of exhaled gases
Postictal inactivation of RAM by REM sleep or cramping
Complete DP from DCC
Acute R > L cardiac shunt from DCC precipitates critical hypoxemia (cardiac arrest)
Survival factors in seizure
Sz does not hyperstimulate respiratory muscles
Sz hyperstimulation of D only (not RAM, which can compensate)
Sz hyperstimulation of RAM only (not D, which can compensate)
Sz hyperstimulation of D is unilateral or partial
Subcritical sz duration re: metabolic derangements (lactate, electrolyte changes), overheating
Subcritical sz/postictal apnea duration re: hypoxemia (no cardiac arrest)
Postictal incomplete excitation of D (still functional) e.g. transient diaphragm spasms but not DCC

Sz: seizure, D: diaphragm, RAM: respiratory accessory muscles, DCC: diaphragm cramp-contracture, OSA: obstructive sleep apnea, DP: diaphragm paralysis; R: right, L: left.

Table 4 – Factors controlling respiratory outcome of nocturnal seizures. It is important to recall the proposed sequence of events hypothesized here in SUDEP: seizure hyperstimulates the respiratory muscles leading to diaphragm fatigue and neuromuscular excitability culminating in respiratory arrest by DCC. But to trigger DCC, there must be a sudden increase in ventilatory workload. Depending on apnea duration and subsequent degree of hypoxemia, cardiac arrest and death could ensue if critical.

Diaphragm involvement in fatal seizures is supported by a SUDEP mouse EMG study in which all deaths also occurred by terminal apnea. The mice carried mutations of a sodium ion channel protein (*Scn8a*) identified from SUDEP patients. It is found in both sensory and motoneurons of the central and peripheral nervous systems. By inducing seizures while measuring D-EMG, *Wenker et al* (2021) [114] discovered terminal apneas occurred by continuous (tonic) diaphragm contractions. Deaths did not occur in those receiving MV. These findings are consistent with seizure-induced DCC. MV was life-sparing perhaps because work of breathing was reduced (no DCC) or if excitation happened, overcame the airway resistance of diaphragm hypercontraction.

A final study supporting diaphragm excitation in seizure comes from a study of 100 children under twelve years old with partial epilepsy using videotaped seizure analysis and data collection during the preictal, ictal and postictal phases [115]. Most of the 514 seizures were localized to the temporal lobe. The entire array of presentations in descending order of frequency included flushing, coughing, *apnea/bradypnea*, *epigastric aura*, *hyperventilation, dyspnea*, hypersalivation, *vomiting*/nausea, spitting, miosis, *hiccups* and *belching*. Although assumed secondary to autonomic causes, nearly all symptoms could rather have related to the diaphragm itself (in italics). In other words, seizure activity could have been carried to the diaphragm by the phrenic nerves. Subsequent diaphragm excitation followed by fatigue, spasms and gastroesophageal clamping could have been responsible. This is supported by a case report of a 6-year-old girl with daily hiccups associated with bilateral myoclonic D-EMG bursts following epileptiform EEG activity [116]. Symptoms resolved with valproate. Epigastric, or visceral aura is a symptom complex of short duration involving ictal abdominal discomfort, nausea and burning sensation. It occurs most commonly with temporal lobe seizures and receives unusual descriptions such as "*fluttering*, pressure, rolling and turning of internal organs". Again, these are consistent with putative diaphragmatic "butterflies" and other mild DHD. However, extreme fear and panic sometimes occur, and perhaps this is not without good reason. Sudden sustained diaphragmatic inactivation by a focal seizure, essentially a broken pump in the face of worsening hypoxemia and hypercapnia causing inability to breathe in a child, would most certainly trigger severe apprehension, panic and an impending sense of doom. Interestingly, such symptoms also occur in abdominal winding injuries.

Diaphragm Spasm and Cramp in Winding Injuries

Like the tympanic membrane of the ear, the diaphragm serves as a hermetic seal between two anatomical compartments under differential air pressures (chest and abdominal cavities) (**Figure 15**). Both seals can rupture from sudden changes in air pressure: the tympanic membrane in SCUBA barotrauma, and the diaphragm in high-velocity blunt impacts to the chest or abdomen (e.g. motor vehicle collisions or falls from great heights). Being winded (celiac or solar plexus syndrome) occurs by a lower velocity blunt blow. It can happen with a punch or kick, a slip and fall onto the back or sometimes, running collisions between NFL football players, one of which who did not brace himself in time (Damar Hamlin "cardiac arrest"). Upon literature review, of which only two old medical textbooks and one reputable web page could be found, diaphragmatic spasm was

mentioned to cause "momentary respiratory paralysis" [117, 118]. No supporting evidence was available unfortunately.
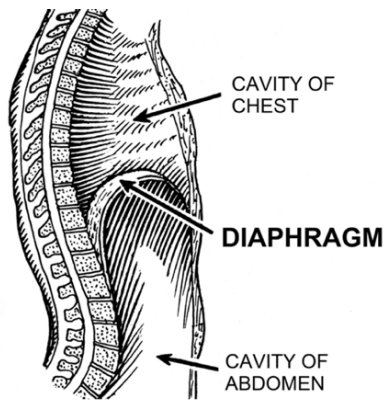
Fig. 15 – Diaphragm anatomy in relation to chest and abdomen (lateral view). The respiratory diaphragm, a hermetic seal like the tympanic membrane of the ear, separates the chest from abdominal cavities. A blunt blow to one is transmitted through the diaphragm to the other. It is prone to rupture in high-velocity trauma but with lower forces (winding injuries), neuromuscular excitation is thought to occur as a diaphragm spasm or persistent cramp. *Source:* Pearson Scott Foresman, Public domain, via Wikimedia Commons, 2008.

Upon chest or epigastric impact in winding injury, kinetic force is likely transmitted to the diaphragm. Although there is immediate pain, the more worrisome symptom is the involuntary forced expiration with sustained apnea (inspiratory arrest). Usually this lasts just a few seconds. However, as above (epigastric aura in focal seizures), the commonly experienced sense of impending doom is perhaps not without good reason. Although most winding injuries are short-lived and seemingly benign from putative transient diaphragm spasms (like those proposed in infantile forced expirations)*, it is conceivable that higher-force injuries could be fatal from prolonged apnea and respiratory arrest by persistent spasm, or DCC. This would be followed by hypoxemic syncope and possibly seizure as well as cardiac arrest and death if not rapidly aborted. Such fatalities would go on to be diagnosed postmortem as traumatic cardiac arrests or commotio cordis, thus missing the primary respiratory pathology. Commotio cordis occurs by a *projectile,* like a baseball or hockey puck, striking the left chest over the heart and inducing ventricular fibrillation and cardiac arrest. This may not necessarily have been the case in the *Hamlin* collision though (by assuming forces were transmitted to the heart yet *without the focal aspect* defined by commotio cordis experiments) [119]. Importantly, CPR priorities differ between the two: cardiac compressions in commotio cordis versus rescue breathing in winding injury arrests.

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* Interestingly, tensor tympani syndrome is a disorder of the middle ear similar to spontaneous diaphragm spasms. Involuntary myoclonic contractions of this small, striated muscle cause a soft clicking or thumping sound as well as hyperacusis and otalgia. And like diaphragm flutter, it can be triggered by anxiety.

In summary, the kinetic forces of blunt trauma transmitted to the diaphragm could trigger neuromuscular excitation in the form of spasms and cramps. Apnea results and its duration would dictate survivability based on the degree of subsequent hypoxemia and potential for cardiac arrest. Moving forward, reproducing winding injuries under experimental conditions in test animals using fluoroscopy could reveal the traumatic forms of DHD.

Diagnosing Diaphragm Fatigue and Excitation in Children

Objective signs of diaphragm fatigue in infants are identical to those of respiratory insufficiency, including tachypnea and laboured breathing, grunting, wheezing, sweating, and rib and subcostal retractions. A suddenly silent chest and paradoxic breathing are late findings. From frequent hiccups and respiratory instability in neonates, to bronchiolitis, apneas, breath-holding spells or life-threatening symptoms in older babies and children (with cyanosis, pallor, hypotonia, altered mental status or brief resolved unexplained events), the various etiologies and parameters of underlying diaphragm fatigue can be identified (**Tables 5 and 6**). This includes labs to rule out anemia, electrolyte disorders and abnormal acid-base balance. Screening tests to reveal diaphragm damage from hypoxia, hyperthermia and myopathic viral infections include serum CPK (creatine phosphokinase or creatine kinase), CK-MM (muscle type creatine kinase) and skeletal muscle troponin-I. Although not specific to respiratory muscles, correlating their levels to changes in clinical state would be helpful. In bronchiolitis, these could screen for those at risk for apneas. Those with elevated levels should be admitted for respiratory monitoring by chest impedance or even better, continuous RIP and transcutaneous D-EMG. In those with respiratory distress, bedside abdominal ultrasound might reveal the supraphysiologic excursions of DHD (e.g., spasms, flutter, cramps). Video fluoroscopy would also provide direct visual evidence of DHD and could be done bedside using a "C-arm". Dynamic chest radiography, a newer technology, offers a better alternative to fluoroscopy because of lower exposure to ionizing radiation. Of special mention, electrical activity of the diaphragm, specifically, high tonic Edi (and prolonged duration into expiration), appears to reflect diaphragm fatigue in MV infants, worsened under increased workloads like bronchiolitis, hypoxemia and after extubation [99]. In spontaneously breathing infants, it might predict respiratory deterioration. D-EMG by esophageal catheter is superior to transcutaneous due to less artifacts from noise and movement. Finally, diaphragm biopsy could be reserved for cases with severe respiratory insufficiency when the diagnosis of diaphragm weakness in neuromuscular disease or DHD are in question. Diaphragm

histology could reveal evidence of infectious diaphragm myositis and myopathy as well as scarring from repeated HE.

Labs tests (screening, trends and respiratory distress[*] PRN)
Nasopharyngeal swab (r/o respiratory viruses)
Hemoglobin (r/o anemia)
Extended electrolytes (sodium, potassium, calcium, magnesium, phosphate)
Lactate and VBG (pH, pCO_2, HCO_3)
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.

*i.e., tachypnea, hypopneas, rib retractions, TAA, recurrent or prolonged apneas, desaturations, bradycardia, cyanosis, pallor, hypotonia, syncope, seizure, unexplained events, frequent hiccups, abdominal pulsations.

Table 5 – Proposed labs to reveal evidence of diaphragm fatigue/excitation, and potential markers.

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[†]
Bedside fluoroscopy ("C-arm") or dynamic chest radiography in active DHD
Diaphragm biopsy (myofiber disruptions, infiltrates, contraction bands, scars)

RIP: respiratory inductive plethysmography, D-EMG: diaphragm electromyography, TAA: thoracoabdominal asynchrony, US: ultrasound, D-CEUS: diaphragm contrast-enhanced ultrasound, DHD: diaphragm hyperexcitation disorder.

*i.e., respiratory distress or lab abnormality (refer to Table 5), SIDS sibling(s).

†Diaphragm spasms, myoclonus, flutter.

Table 6 – Proposed monitoring and imaging to reveal evidence of diaphragm fatigue/excitation.

Treating Diaphragm Fatigue and Excitation in All Ages

Table 7 provides emergent interventions and potential medications identified on preliminary literature review that might improve DD, and thus prevent or attenuate excitation. In patients of any age with respiratory distress or infants with ventilatory instability, this includes correcting anemia, electrolyte disorders and acidosis as well as providing supplemental oxygen, rehydration and antipyretics as needed. In addition, it might be prudent to stop anti-reflux medications until phosphate and magnesium levels are confirmed normal. Methylxanthines such as caffeine and theophylline have been used for over 50 years to reduce apneas-hypopneas and HE in infants. These are thought to

stimulate the CNS respiratory centers, however, also have peripheral effects at the respiratory muscles [120, 60]. Chlorpromazine, an older antipsychotic dopamine antagonist with relaxation effects on the CNS and skeletal muscles, was most commonly used to treat DHD, particularly effective in intractable hiccups and respiratory flutter [13]. Its calming effect might even reduce diaphragmatic hypertonicity in extreme anxiety. N-acetylcysteine has shown promise by improving diaphragm force-generating capacity and demonstrating anti-inflammatory activity in a mouse model of muscular dystrophy [121]. Finally, diaphragm pacing might prevent or treat unstable DHD.

Treatment is a high priority in OSA because of serious comorbidities. But despite the ubiquitous use of positive airway pressure masks that improved OSA severity (e.g., CPAP and nasal masks), long-term benefits such as reduced hypertension in adults were minimal [122]. Instituting therapies tailored to reducing respiratory muscle fatigue and workload offer a novel approach.

General interventions	Potential medications
Supplemental oxygen	Caffeine, theophylline
Intravenous access	Chlorpromazine, haloperidol
Cardiac monitor, RIP, oxygen saturations, capnography	SSRIs
CPAP, nasal mask, intubation & mechanical ventilation	Gabapentin, pregabalin
Minimize psychiatric stressors and pain	Carbamazepine, phenytoin, levetiracetam
Anti-seizure medications PRN	Benzodiazepines, amobarbital?
Correct hypovolemia and acidosis (bicarbonate?)	Cyclobenzaprine
Correct anemia and electrolyte disorders	β-agonists[*]
Stop antireflux medications (Mg and Phos)	CACB[†]
Treat infection (antibiotics, antivirals?)	ACE inhibitors
Treat bronchospasm (β-agonists, theophylline?)	Pentoxifylline
Body cooling measures PRN	N-acetylcysteine
Diaphragm or phrenic nerve pacing	Erythropoietin
	Lidocaine?

RIP: respiratory inductive plethysmography, CPAP: continuous positive airway pressure; PRN: pro re nata (as necessary); SSRIs: selective serotonin reuptake inhibitors; CACB: calcium channel blockers; ACE: angiotensin-converting enzyme; *salbutamol, terbutaline, isoproterenol, procaterol; †nicardipine, verapamil, nifedipine.

Table 7 – Treatment of emergent diaphragm fatigue/excitation in respiratory distress. Generalized interventions (left). Medications obtained upon literature review (right) are only preliminary findings, not corroborated. Some are active at both CNS and respiratory muscles.

Diaphragm Pathology in Decompensating Medical Conditions and Cardiopulmonary Arrest

There are a wide variety of emergent medical conditions appearing to share in common terminal respiratory decompensation and sudden arrest, consistent with DD and DCC, respectively. Many have already been discussed. Recognizing this, especially in "matter of life and death" situations, offers an opportunity for clinicians to immediately institute treatments that could improve ventilatory muscle function. **Supplemental Table 3** lists these conditions along with supporting citations. Some examples are provided here.

Well-known chronic illnesses terminating in end-stage respiratory distress include a wide variety of neurologic and myopathic diseases, such as amyotrophic lateral sclerosis, myasthenia gravis and muscular dystrophy. Other emergent conditions include asthma, COPD, pneumonia and sepsis as well as bronchiolitis and severe gastroenteritis dehydration in children (hypovolemic shock with acidosis). Other shock states include hemorrhagic, neurogenic and cardiogenic (the latter by myocardial ischemia, myocarditis, arrhythmias, pulmonary embolism or cardiac tamponade for example). Survival could also be improved in severe acidosis, such as diabetic, starvation and alcohol ketoacidosis as well as metformin lactic acidosis and toxicities from methanol, ethanol and ethylene glycol. Less common conditions include respiratory complications of malignant hyperthermia, anesthesia induction, pheochromocytoma crisis, tetanus, rabies and malnourishment. Traumatic examples include diaphragm weakness from birth asphyxia and cervical soft tissue injuries as well as severe winding injuries, traumatic and restraint cardiac arrests and crush syndrome. Exposures include heatstroke, cold water near-deaths (near-drownings and submersions) and survivors of electrocutions and conducted electrical devices (tasers and stun guns). Finally inclusive are those with severe or prolonged seizures.

To best combat the respiratory arrest of DCC, CPR guidelines need to be revisited, for both healthcare professionals and the community. In all pediatric and winding injury cardiopulmonary arrests, advanced pediatric and trauma life support should first focus on the airway and breathing before chest compressions, given the cause is almost always a respiratory emergency. CPR education should stress the importance of opening and maintaining a patent airway and administering effective rescue breaths by visually confirming chest rise (this is not explicitly stressed in the current guidelines). Also essential is to overcome the initial airway resistance of DCC and not fear overinflating the lungs until this is accomplished.

Conclusions

It is exceptional the wealth of information that stemmed from only two symptoms in a solitary patient, let alone one who survived their repeated near-death experiences starting when just 7 years old while in bed alone. He overcame the paroxysmal bearhug pain apnea episodes, deduced to be spontaneous diaphragm cramps, because his wherewithal and troubleshooting ability ultimately led to impromptu rescue breaths that overpowered the tension of muscle contracture. Literature evidence for novel DCC in sudden unexpected deaths is highly compelling, albeit indirect for the time-being, as this mechanism of respiratory arrests hides from plain sight both *in vivo* and postmortem.

Some of the best support was provided by EMG studies in preterm infants with apneas, demonstrating simultaneous failure of diaphragm and RAM (*Lopes et al*), and in adult sleep apneas, abnormal diaphragm electromechanical activity (dissociation) (*Luo et al*). Dr. Eisenhut's evidence of diaphragm myositis-myopathy in an infant with RSV respiratory arrest was also quite significant. *Siren and Siren's* papers helped build the foundation supporting DCC as a potential complication of critical diaphragm fatigue. Case reports of persistent hiccup, diaphragm spasm and flutter revealed the existence of various hyperexcitable disorders (DHD), many of which are triggered by psychological distress. Moreover, they presented along a novel frequency spectrum correlated to worsening symptoms and prognosis. Critically unstable DHD included high frequency, tetanic contractions of nicotine toxicity and certain electrocutions. Along with DCC, these were thought to occupy the severe end of the spectrum.

In general, sudden inspiratory arrests by acute diaphragm paralysis are an underrecognized cause of serious morbidity and mortality in all ages. If the apnea is unrecognized in adults, they would be misclassified as sudden cardiac deaths. The paralysis, which is already known to occur with nicotine, succinylcholine and bilateral phrenic nerve injuries, for example, can be immediately fatal when it is bilateral, neurologically complete and affects those with weak or inactivated accessory muscles. Also, it needs to be sufficiently long as to induce cardiac arrest by critical hypoxemia. This too was a novel finding that could be responsible for some SIDS cases, because DCC satisfies all such criteria. Optimistically, this provides a window of opportunity to recognize DCC in sleeping infants by improving respiratory monitoring techniques and rapidly instituting ventilatory assistance.

Diaphragm fatigue and excitation are central to the DCC hypothesis in SIDS (as well as non-arrhythmogenic sudden unexplained deaths in all other ages). Diaphragm fatigue, the outcome of mismatched metabolic supply and demand — which appears to occur more

often in males than females — is exacerbated by hypoxemia and numerous other endogenous and exogenous factors that generally impair diaphragm contractility, prolong its relaxation or increase ventilatory workload. These overlap with most, if not all, SIDS risk factors. Endogenous ones include male sex, prematurity, prone position, REM-sleep RAM inactivation and upper airway muscle obstructions as well as fever, sweating, pneumonia, bronchiolitis, bronchospasm, dehydration, electrolyte disorders, acidosis, anemia and seizures. Exogenous factors include nicotine, over-bundling, rebreathing, viral infections and bacterial toxins in sepsis. Consequent diaphragm insufficiency reduces alveolar ventilation. This perpetuates the hypoxemia (hypercapnia and respiratory acidosis as well), leading to escalating fatigue in an unstable, positive feedback cycle. Simultaneously, anemia and diaphragm hypoperfusion from dehydration or hypotension would exacerbate the DD because of reduced delivery of oxygen and metabolic substrates like glucose, fatty acids and electrolytes. In experimental septic and cardiogenic shock in spontaneously breathing test animals, hypotension led to rapidly progressive diaphragm fatigue, abruptly terminating in respiratory failure. Although the terminal mechanism could not be elucidated, it was most likely due to failure of the contractile machinery. Also, the deaths were sudden and rapid, all consistent with DCC (and SIDS).

Prolonged diaphragm relaxation by fatigue, ryanodine, acidosis and endotoxins predisposed to neuromuscular irritability in the form of diaphragm contractures *ex vivo*. By extension *in vivo*, diaphragm fasciculations, spasms, cramps and flutter could develop, particularly under higher respiratory rates when relaxation takes longer than the expiration phase of the ventilatory cycle. Excitation in fatigued skeletal muscles is known to be triggered by workload surges. In sleeping infants, this could occur in the diaphragm by a roll to prone position, REM-sleep onset, bottle feeding or even psychological distress. This could tip the balance from critical fatigue to failure by DCC, ultimately causing a respiratory emergency.

Many of the breathing issues common to preterm infants, such as apneas-hypopneas, hypoxemic-cyanotic episodes, periodic breathing and even frequent hiccups, can all be explained from a diaphragm excitation standpoint (rather than abdominal muscle contractions or CNS dysfunction). The same can be said of OSA in all ages. The novel obstruction of OSA, proposed here, develops when RAM contractions to breathe are resisted by the temporarily inactivated, hypercontracted diaphragm of spasm. Airway obstructions by atonic supraglottic muscles would only contribute because of the added fatigue.

At the histological level in SIDS at autopsy as well as rapid deaths in RSV bronchiolitis, diaphragmatic myositis-myopathic changes already provide a starting point to uncover evidence of the anoxic hypercontraction injury thought to be DCC itself. Therefore, **diaphragm histology needs to be done at autopsy**. Critical acidosis and extreme hyperkalemia were reported but never corroborated. Along with other electrolyte disorders, these would predispose to DCC through their various pathological effects on excitation-contraction coupling.

In adults with OSA, putative diaphragm hypertonicity-excitation-clamping of the IVC and aorta could explain many of its known complications, such as pulmonary and systemic hypertension, cardiomyopathies, pulmonary edema and a host of other serious cardiovascular disorders. In spasms, such acute changes would be transient and modest, whereas in flutter or DCC, persistent and more severe. Increased diaphragmatic tone in acute anxiety, if confirmed, would represent a novel connection between mind and body. Epigastric "butterflies" could be such a manifestation. Moreover, esophageal clamping would explain the host of gastrointestinal symptoms common to anxiety, also reported in diaphragm flutter and even some pediatric temporal lobe seizures. In the latter, we proposed CNS seizure activity transmitted by the phrenic nerves hyperstimulates the diaphragm causing periictal hyperpneas and hypopneas-apneas leading to net hypoxemia. Subsequent diaphragm fatigue would be worsened by prone positioning and postictal tachypnea. Critical hypoxemia, hyperacute acidosis or REM-sleep could be the final trigger leading to DCC respiratory arrest, ultimately causing a rapid, silent death consistent with SUDEP. Finally, winding injuries appear to induce forced-expiration inspiratory apneas by diaphragm spasm or DCC, depending on severity. Like infantile expiratory apneas, the former is thought to be transient whereas the latter, persistent. Apnea duration would dictate degree of hypoxemia and risk for syncope, secondary cardiac arrest and death. This would mimic commotio cordis and other traumatic cardiac arrests and is important for future studies to distinguish because CPR priorities differ.

Astoundingly, thumb-sucking appeared to have spared our case patient's life (prior to his first DCC episode after ceasing the habit). Pacifiers (and likely digit-sucking), which are known to be SIDS preventative, might reduce diaphragmatic workload or minimize ventilatory pausing at end-expiration, when DCC reportedly strikes. Autoresuscitation in the case patient apparently occurred by breathing out to breathe in, augmented by positive-pressure inspirations. CPR in DCC respiratory arrests needs to focus on maintaining a patent airway and confirming adequate rescue breaths while overcoming the initial airway resistance.

Screening labs for diaphragm injury and excitation include venous gases and CK-MM or sTnI, although these are not specific to respiratory muscles. Regardless, they might risk-stratify infants with RSV and other viral infections for prolonged apneas. The same would apply to former preterm infants about to be discharged from the neonatal ICU. Bedside tests in active DHD include diaphragm ultrasound and fluoroscopy. Respiratory monitoring could be accomplished by continuous RIP or D-EMG. Therapeutics for diaphragm fatigue include caffeine, CPAP and chlorpromazine amongst others. The latter offers a novel approach to prevent and treat respiratory instability in infants as well as OSA in all ages. Diaphragm pacing might avert unstable diaphragmatic arrhythmias in high-risk individuals. Above all else however, **DCC needs to be reproduced and confirmed experimentally**.

Figure 16 depicts the overall DCC pathogenesis in SIDS. **Figure 17** demonstrates the numerous causes of diaphragm fatigue discussed here. The *Patient's Perspective* and supplemental materials are also provided in the appendix below.
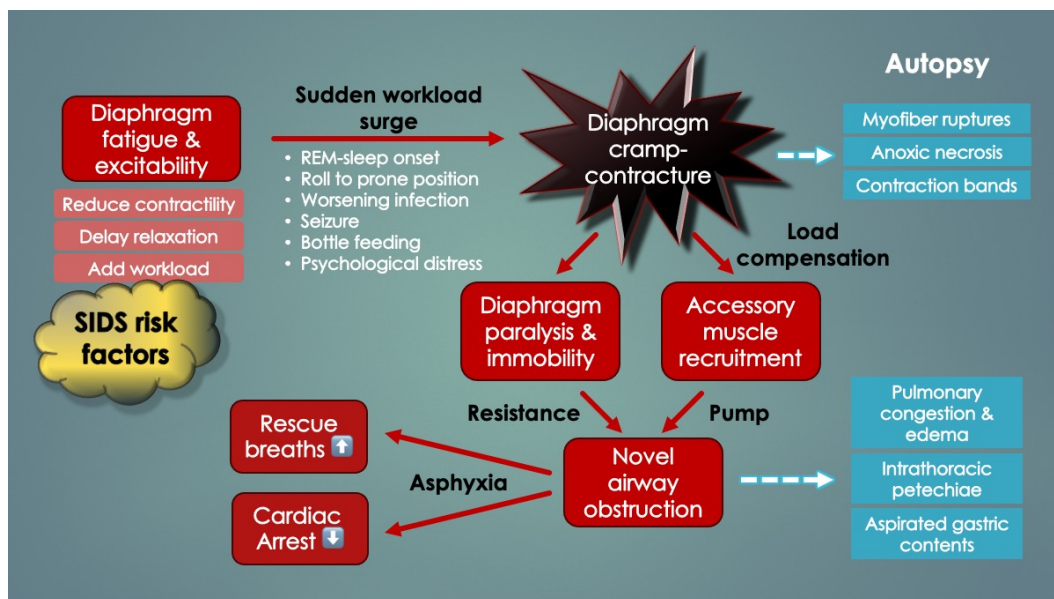
Figure 16 – Proposed diaphragm cramp-respiratory arrest pathogenesis in infants. Most, if not all, SIDS risk factors fatigue the diaphragm, increase its workload or delay relaxation. Increased tonicity and excitation develop in skeletal muscles when fatigued, and respiratory muscles like the diaphragm are likely not exempt. Diaphragm cramp is thought to be triggered by ventilatory work overload when fatigued. A novel airway obstruction would develop where the paralyzed diaphragm resists inspiratory efforts by agonal RAM contractions. Postmortem findings consistent with DCC include disrupted myofibers and anoxic contraction band necrosis (both of which are visible only microscopically) as well as signs of asphyxia by terminal airway obstruction. Respiratory arrest can be reversed by rescue breaths, but the window of opportunity is short given cardiac arrest will ensue within minutes.
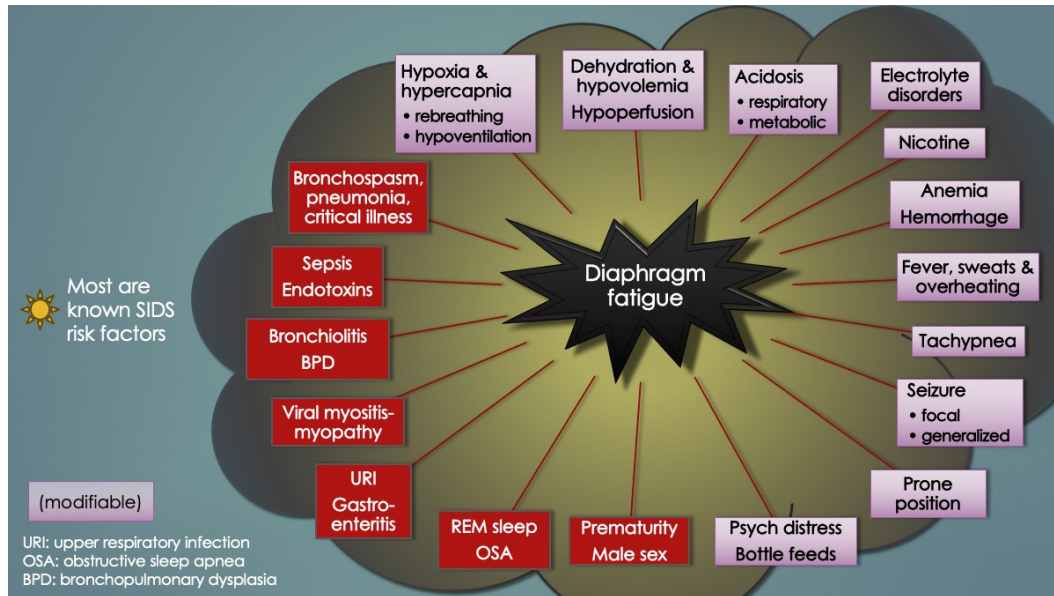
Figure 17 – Diaphragm fatigue/excitation factors. These overlap with known SIDS risk factors. Some are modifiable, like giving oral fluids for dehydration, blood transfusions in anemic apnea and avoiding nicotine exposure.

Sincerely,

Dov Jordan Gebien and Michael Eisenhut

APPENDIX

Patient's Perspective <return to text>

This account was written by the case patient, who is a practicing medical doctor born in 1970 (52 years old at disclosure). With trauma counselling in 2022, he explored 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 defense (survival) 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 a sharp and excruciating 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 also baffled because my mouth had opened involuntarily when I first 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 that nobody was there. The bearhug and inability to inhale (inspiratory apnea) persisted.

Despite the impending sense of doom I began troubleshooting by experimentation. But when I tried inhaling more forcefully it was met with equal and opposite, complete resistance to airflow. It was futile. My next test, to exhale, was successful though and I remember telling myself not to lose all the air in my lungs so to conserve it. I still couldn't breathe in, and the pain continued. I was not panicked and did not have stridor, choking, fullness or a foreign body sensation in my throat.

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 [see **Video S1** for more]. To my relief, the pain and apnea resolved immediately, and normal breathing resumed. Crisis averted, so I went back to sleep *as only a seven-year-old can despite a near-death experience*. Soon afterwards, I noticed a pilot on TV spinning in a centrifuge using 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 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, I did have a fair bit of diarrhea throughout my childhood and youth of unknown cause.

Eventually I 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. I can say with absolute certainty, the pain was a muscle cramp. I should also note the bearhug came on

just at the *very end of expiration* (if not averted by quickly breathing in). 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 upon the next breath.

The rescue breaths were so loud and high-pitched, I remember being awakened one night by the sound. It appears I had grown so accustomed, that *I did them in my sleep*. Oddly, I also recall telling myself to keep it quieter the 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 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 definitely treated a congenital hiatal hernia. I recovered well, quickly gained weight and do not recall having reflux symptoms as I grew older.

Since age 8 or 9 years, I frequently experience painful fasciculations and muscle cramps that cause contracture-like stiffness in the affected limbs. 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 prevent imminent cramps 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 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 smoker. Brother denied sleep-related pain, breathing issues 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 onset of the breathing emergencies (important because pacifiers are SIDS protective). I cannot think of anything else that had changed which could explain why this all started at age 7 and not sooner (how fortunate I am)!

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."

<p align="center">* * *</p>

I may have survived these life-threatening events because, as opposed to an infant, I had the benefit of wherewithal and 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.

Supplemental Tables

Table S1   [return to text]

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)

Table S1 – 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 onset, cramp-like bilateral rib (bearhug) pain with simultaneous complete apnea. Deductive reasoning yielded five final diagnoses of varying clinical confidence.

Table S2   <return to text>

Table S2 – 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 respiratory arrest in individuals with critical diaphragm fatigue, primarily young infants because of underdeveloped respiratory muscles. It is thought to be sudden, silent and rapidly progressive, with only 5-10 s before hypoxic syncope and cardiac arrest ensue (1-2 min). It can be aborted by autoresuscitation (breathing out to breathe in) or bystander rescue breaths.

Traumatic DCC (t-DCC) is thought 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 (cramp). As above, this would rapidly progress to syncope, cardiac arrest and death if not aborted. In contrast, milder winding injuries cause brief, forced apneas from *transient* diaphragm spasm (commonly experienced in martial arts for example).

1	Compared to the other vital pump (heart), the diaphragm has been grossly understudied and underappreciated as causing serious disease.
2	s-DCC respiratory arrest is thought to have exceptionally high mortality (few survivors who live to tell about it). The most commonly affected age group is infants (preverbal). Also, nocturnal cases are triggered in REM-sleep, a deep sleep stage that makes recall of events less clear.
3	It is silent because of inspiratory arrest. Victim unable to cry out for help. Death occurs rapidly (about 5 min post-respiratory arrest) and is unwitnessed in most cases.
4	DCC is not visible, because the diaphragm is an internal organ. Also, evades detection by most electrophysiological studies.
5	The respiratory arrest mimics other conditions, such as choking, seizure and collapse from sudden cardiac arrest, leading to misclassification of the critical apneic event.
6	Similar to malignant arrhythmias like VFib or VTach, pathological excitation of pump muscles do not persist postmortem (at autopsy). Also, the airway obstruction of DCC is not visible, as the offending agent is the diaphragm itself.
7	Standard autopsies in sudden death cases generally inspect the diaphragm grossly but omit histology (thus missing the myositis/myopathic changes of DCC) . No gross abnormalities are detectable.
8	In non-monitored inpatients, critical apnea is silent and easily avoids detection. Even in those receiving respiratory monitoring, airflow is not measured; rather chest impedance (respiratory movements). 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 do not receive immediate attention (as does cardiac arrest). Therefore, it is plausible the *apnea of DCC is being missed in both settings*. In addition, oxygen desaturation alarms are a late finding, missing the critical event.
9	In t-DCC, respiratory arrest, syncope and collapse can be mistaken for traumatic cardiac arrests (asystole, VFib, VTach) or commotio cordis (VFib). [This is important because their CPR priorities differ (chest compressions vs. rescue breaths in DCC).]
10	Those who survive hypoxic syncope from t-DCC will likely have retrograde amnesia, unable to recall the respiratory arrest (e.g. collapse of NFL player in 2023).

DCC: diaphragm cramp-contracture, VFib: ventricular fibrillation, VTach: ventricular tachycardia

Table S3   <return to text>

Table S3 – Acute and chronic medical conditions that can present emergently with respiratory decompensation by critical diaphragm fatigue. Upon literature review, many fatalities had exhibited terminal apnea prior to cardiac arrest. This could have occurred by central or peripheral causes. However, only the latter was demonstrated in experimental septic, cardiogenic and hypovolemic shock, from "fatigue-induced failure of the [inspiratory] contractile machinery" (consistent with the DCC mechanism). Corresponding citations in green are provided below.

Condition	Citation
Neurologic & myopathic	
Neuropathy (e.g. ALS, GBS, myasthenia gravis)	[1]
Myopathy (e.g. MS, muscular dystrophy, polymyositis)	[2]
Critical-illness polyneuropathy	[3,4]
Generalized tonic-clonic and focal seizures	[5,6]
Lower and upper airway	
Asthma, COPD, pneumonia	[3,4,7]
Bronchiolitis	[8]
Croup, acute epiglottitis, bacterial tracheitis	[9]
Acute lung injury, ARDS	[10]
Cystic fibrosis	[11]
Infection	
Influenza and other viral URI	[12,13]
SARS-CoV-2 (COVID-19)	[14]
Severe gastroenteritis dehydration	[15,16]
Rabies and tetanus, Lyme disease, polio	[3]
Shock	
Septic	[17,18]
Hypovolemic	[19,20]
Hemorrhagic	[21]
Cardiogenic (e.g. AMI, arrhythmias, PE, tamponade)	[19,22]
Neurogenic and noncardiogenic pulmonary edema	[23]
Metabolic acidosis	
DKA, lactic acidosis, starvation ketosis	[24,25]
Toxicities (e.g. metformin, methanol, ethanol, ethylene glycol)	[26]
Medications and neurotoxins	
Malignant hyperthermia	[27,28]
Succinylcholine and anesthesia induction	[29]
Nicotine, botulism, tetanus, curare	[30,31]
Envenomations, neurotoxins	[30,31]
Aminoglycoside antibiotics	[32]
Endocrine & electrolyte disorders	
Pheochromocytoma, catecholamine storm	[33]
Thyroid, parathyroid hormones	[34]
Corticosteroids and aldosterone	[34]
Diabetes, hyperglycemia	[34,35]
Hyperkalemia (and extreme acidosis)	[36]
Hypokalemia	[37]
Hypomagnesemia	[38,39]
Hypophosphatemia	[40]
Hypocalcemia	[41]
Hypercalcemia	[42]
Hyponatremia	[43]
Hypernatremia	[44]
Trauma	
Phrenic nerve injuries: birth trauma, soft tissue injuries	[45,46]
Diaphragmatic injuries: rupture, laceration, contusion, paralysis	[47,48]
Cervical spinal cord injuries	[49]
Severe winding injuries, traumatic cardiac arrests	[50,51]
Exposures	
Electrocutions	[52,53,54]
Mechanical asphyxiation (e.g. restraint cardiac arrest, crush syndrome)	[55,56]
Heat stroke/hyperthermia (e.g. vehicular, marathon runner arrests)	[57,58,59]
Chemical asphyxiants, inhalational injuries	[60,61]
Heatstroke, cold water immersion and near-drownings	[62,63,64]
Barotrauma	[65]
Other	
Malnourishment	[25]

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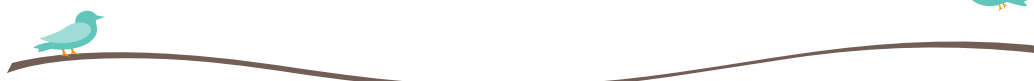
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Supplemental Figure 1 <return to text>
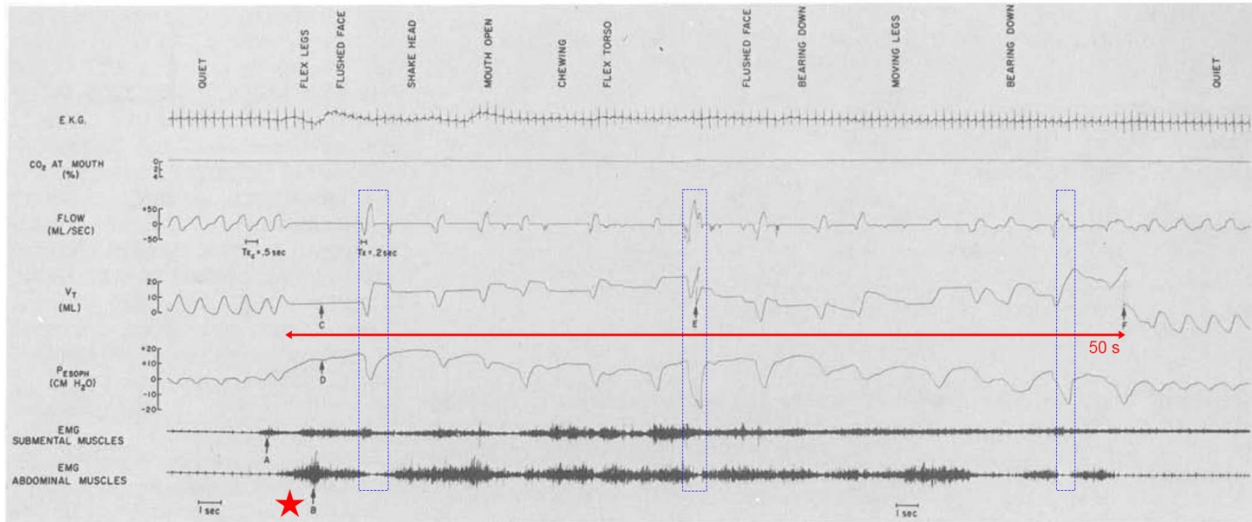
Figure S1 – Sleep polysomnograph including *surface* electromyography (EMG) in a preterm infant with silent squirming and respiratory instability (full image). In addition to tidal volume (V_T) and airflow, important parameters include esophageal pressure (P_{ESOPH}) and abdominal muscle EMG (EMG_{ABDO}). Oxygen saturations not available. An abnormal sequence begins at "A-B" (red star), where EMG_{ABDO} activity was followed by a slow rise in P_{ESOPH} ("D"), both of which remained abnormally elevated for 50 s until the end of the episode. Simultaneously, normal tidal breathing was interrupted at "C" by a 4 s apnea, associated with silent squirming (flexing legs, flushing, etc.). This was followed by a stepwise, breath-to-breath increase in end-expiratory volume consistent with breath stacking (occurred twice and required downshifting at "E" and "F" to stay on scale). Unusually, these respirations (seen in V_T and Flow) were reversed in which *expiration preceded inspiration* (not discussed by authors). Respirations were also slowed (bradypnea) and of lower volumes (hypopneas). Despite elevated EMG_{ABDO} and P_{ESOPH}, negative deflections in the latter (and hypopneas) likely reflect a composite of inspiratory work by the diaphragm and accessory muscles mediated by neural breathing (but not abdominal muscles as they are expiratory). When short, <1 s, pauses in EMG_{ABDO} occurred (blue boxes), unusually large, hyperpneic breaths were taken, perhaps compensation to developing hypoxia and hypercapnia. When EMG_{ABDO} finally abated ("F"), normal tidal breathing resumed. EMG_{ABDO} was interpreted to be from abdominal muscle activity, perhaps by intentional "Valsalvas" (to blow off excess air from hyperinflation). Alternatively, it could reflect *cross contamination by diaphragmatic contractions* given this was measured transcutaneously. Either muscle group could elevate P_{ESOPH}. In other words, diaphragm spasms could have caused the silent squirming episode with its hypoventiliations, breath stacking, hyperinflation and reversed respirations. Finally, the latter is reminiscent of the case patient's rescue breath technique. Perhaps the reversal was intentional. Cite: Abu-Osba YK, Brouillette RT, Wilson SL, Thach BT, 1982. Breathing pattern and transcutaneous oxygen tension during motor activity in preterm infants. *Am Rev Respir Dis*. Apr;125(4):382-7. pp382-387. The American Journal of Respiratory and Critical Care Medicine (previously known as The American Review of Respiratory Disease) is an official journal of the American Thoracic Society.

Video S1 – Rescue breath technique.   <return to text>

Dr. Gebien demonstrates the patient's rescue breath technique by exhaling first, followed by three short-burst, positive-pressure inspirations using his tongue to completely occlude the airway by percussing the hard palate. The case patient recounted how this resembled "a pilot breathing in a centrifuge" (prevents compression of the lungs under centripetal forces). Available at: https://youtu.be/3lWcsamOYOw.
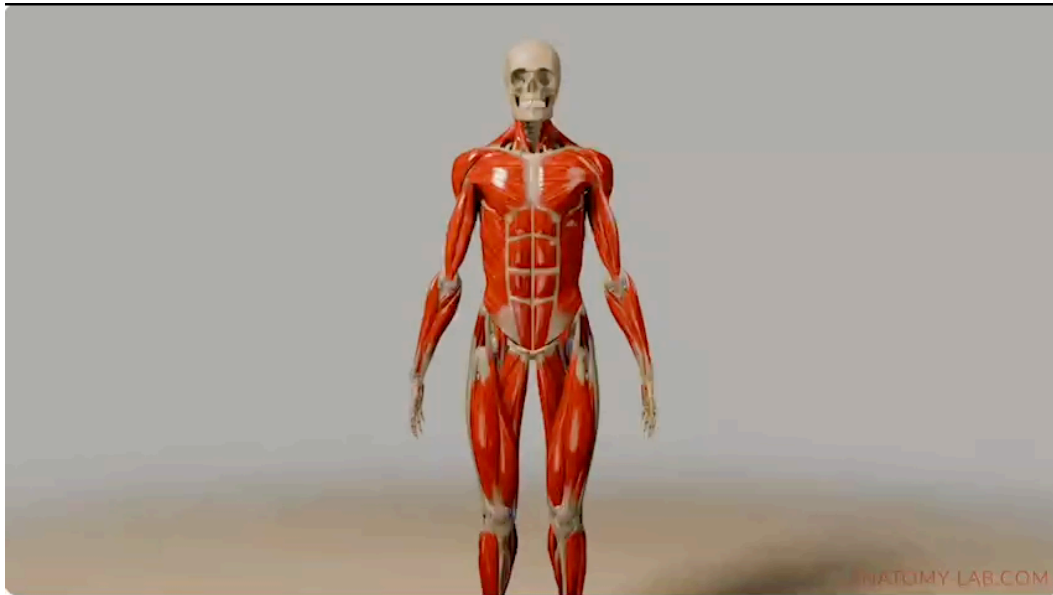
Video S2 – Diaphragm movements animation.

When the diaphragm contracts, it moves caudally thereby expanding ribcage and lungs. Relaxation is mostly passive, however, respiratory breaking (expiratory grunting) in young infants occurs by persistent diaphragm contractions extending into early expiration. *(Double click image to view video)* Available at: https://www.youtube.com/watch?v=Y0W_sueD3Gc. From Anatomy Lab (@AnatomyLab) on YouTube.

<u>Publications by Gebien</u>

- Gebien DJ, Eisenhut M. Diaphragmatic cramp-like contracture (DCC) – a novel terminal mechanism in sudden unexpected deaths of all ages. *ResearchGate*. (2023). https://tinyurl.com/diaphragm-cramp. **Submitted** to *Frontiers Peds* (May 2024).

- Gebien DJ. Myositis "diaphragm cramp" as a potential cause of respiratory arrests in infants. *Diagnostics* 2024, *14*, 601. PMID: 38786359. **Published.** *Comment* re: Salfi et al. Fatal deterioration of a respiratory syncytial virus infection in an infant with abnormal muscularization of intra-acinar pulmonary arteries: autopsy and histological findings. *Diagnostics (Basel).* 2024**.** PMID: 38535022. https://www.mdpi.com/2075-4418/14/10/1061.

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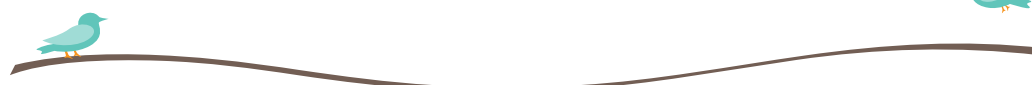
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