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The Sudden Infant Death Syndrome mechanism of death may be a non-septic hyper-dynamic shock

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ABSTRACT

Background: Sudden Infant Death Syndrome (SIDS) mechanisms of death remains obscured. SIDS' Triple Risk Model assumed coexistence of individual subtle vulnerability, critical developmental period and stressors. Prone sleeping is a major risk factor but provide no clues regarding the mechanism of death. The leading assumed mechanisms of death are either an acute respiratory crisis or arrhythmias but neither one is supported with evidence, hence both are eventually speculations. Postmortem findings do exist but are inconclusive to identify the mechanism of death.

What does the proposed hypothesis based on?: 1. The stressors (suggested by the triple risk model) share a unified compensatory physiological response of decrease in systemic vascular resistant (SVR) to facilitate a compensatory increase in cardiac output (CO). 2. The cardiovascular/cardiorespiratory control of the vulnerable infant during a critical developmental period may be impaired. 3. A severe decrease in SVR is associated with hyper-dynamic state, high output failure and distributive shock.

The hypothesis: Infant who is exposed to one or more stressors responds normally by decrease in SVR which increases CO. In normal circumstances once the needs are met both SVR and CO are stabilized on a new steady state. The incompetent cardiovascular control of the vulnerable infant fails to stabilize SVR which decreases in an uncontrolled manner. Accordingly CO increases above the needs to hyper-dynamic state, high output heart failure and hyper-dynamic shock.

Conclusions: The proposed hypothesis provides an appropriate alternative to either respiratory crises or arrhythmia though both speculations cannot be entirely excluded.

Introduction

Sudden unexpected infant death (SUID) is defined as death of an apparently healthy infant less than one year old of no immediate obvious cause, generally during sleep [1,2]. SUID is categorized to 'Diagnosed SUID', 'Sudden Infant Death Syndrome (SIDS)', and 'Undetermined SUID'. In 'Diagnosed SUID', a definite underlying cause is eventually identified either of natural manner of death (e.g. infection, sepsis, congenital cardiac malformation etc.) or accident or infanticide. In Sudden Infant Death Syndrome (SIDS), no explanation is found on comprehensive evaluation including medical history review, inspection of the death scene (sleep environment), and complete standardized autopsy [1,2]. In 'Undetermined SUID' the underlying cause of death remains unclear, as a comprehensive evaluation was not fully conducted.

The most accepted theory of SIDS pathogenesis is the Triple Risk Model which proposes that a triad of key factors must be present simultaneously: Individual subtle vulnerability, critical developmental

Abbreviations: ALTE, apparent life-threatening event; BRUE, brief resolved unexplained event; CO, cardiac output; RV, right ventricle; SIDS, Sudden Infant Death Syndrome; SUID, sudden unexpected infant death; SVR, systemic vascular resistance

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period, and a stressor that triggers the course of events (e.g., hypoxia, hypercapnia, hyperthermia, infection, fever, inflammation etc.) [3].

Prone sleeping had been recognized as a major risk and accordingly the "back to sleep" educational campaigns (latter entitled "safe to sleep") led to a 50% drop in SIDS incidence rates in the western world [1,4–6]. The majority of SIDS cases still occur in prone position [7]. However, prone sleeping per-se cannot explain death nor does it provide clues regarding the mechanism of death.

Several researchers speculated that prone sleeping impairs respiration (e.g. increase intra-thoracic pressure, lower tidal volume or increase respiratory effort). Others suggested it increase the arousal threshold [8], impair the swallow response [9], impair circulatory control during sleep [10], or associated with less effective thermoregulation [11]. It may hamper the infant's "self-rescue" response (e.g. turning the head, kicking the blanket, crying loudly, etc.). Prone position was also associated with accidental suffocation [12] and rebreathing of expiratory air [13]. Prone sleeping had also shown to have a worsening modifying effect on other risk factors (which may increases considerably the individual baseline risk) [1]. However, all these speculations as many other speculations in the literature regarding prone sleeping are insufficient to explain death.

Several pre-morbid conditions were proposed over the years to be associated with SIDS including cardiovascular abnormalities [4,14–16]. Infections in general and undiagnosed sepsis in particular were repeatedly suggested [17–20]. There are many clues supporting the infection paradigm but it lack solid evidence. Metabolic genetic morbidities, diverse mineral abnormalities and vitamins were proposed [4,21,22]. Allergy was also suggested (e.g. house dust mite [23]) and immunological morbidities such as hypogammaglobulinemia and an adverse association between immunoglobulin levels and SIDS incidence [24]. It had been suggested that SIDS is associated with preserved fetal reflexes [25]. This contradicts the relatively low SIDS incidence rate immediately after birth reaching peak incidence only between 2 and 4 months. All the above lack evidences on how do they eventually cause or explain death in the vast majority of cases.

Recent decades' studies consistently demonstrated that SIDS victims carry an anatomic-physiologic brain impairment of the neurotransmitters activity in general and serotonin in particular [2,26–32]. These neurological abnormalities were suggested either to adversely affect the cardio-respiratory control [33] or impair the arousal response [34]. However, these abnormalities in isolation neither explain the mechanism of death nor even explain death.

Many publications had identified or proposed diversity of risk factors that may be categorized to several groups; demographic, socioeconomic, ethnic, parental competence, parent behavior during pregnancy, geography, genetic [21,22], time of onset, sleep arrangements, bedding and clothing, outdoor and indoor climate, residency characteristics such as altitude, prematurity etc. Some of the above may be risk factors or have a worsening modifying effect, but are insufficient to cause or even to explain death. Unnatural causes are not assumed to explain the vast majority of SIDS cases.

SIDS assumed mechanisms of death

Generally, the term sudden death refers to non-violent, unexpected death occurring less than 24 h from the onset of symptoms [35]. The time-to-death in SIDS is much shorter as SIDS infants were found dead after being put to sleep apparently healthy (given infant sleep span is three to four hours). Moreover, the majority of infants (60%) were inspected during sleep, found alive and seemed apparently well, which raise no concern just 2 h before found death [36]. Thus, death may be due to either an abrupt fatal event leading to "immediate death" (within few minutes) or a very short devastating deterioration leading to "fast death" (within very few hours).

Several mechanisms of death had been speculated, predominant by either acute respiratory crisis or arrhythmia.

Acute respiratory crisis was suggested either upper airway obstruction due to anatomical abnormalities or central apnea [37,38]. However, there are no postmortem reports supporting airway obstruction in SIDS but rather nonspecific upper respiratory tract findings. The presumed obstruction may be either positional or due to an external factor (e.g. unnatural death). There are no evidence of a clear link between apnea and SIDS. Accordingly, apnea of prematurity, apparent life threatening event (ALTE) and brief resolved unexplained event (BRUE) have generally been discounted as related with SIDS owing to a lack of evidence [2]. Poets et-al had performed home event recordings of infants and young children with recurrent apparent life-threatening events [39]. The findings provide no clues associating ALTE with SIDS. Moreover, apnea was not proved as a major underlying cause in ALTE. However, apnea is still persistently perceived the predominant SIDS paradigm not only among the general public but also among professional caregivers.

The second frequent speculation as SIDS mechanism of death is dysrhythmia which is questionable in an infant who lacks underlying abnormalities or preexisting pathologies such as coronary abnormalities, cardiomyopathy, conductive or arrhythmic disorders (e.g. Brugada syndrome, Wolf-Parkinson-White syndrome etc.) [4,15]. There is no evidence of convincing association of conductive or arrhythmic genetic variants with SIDS (but rather to less than 10%) [4].

Some researchers had suggested that SIDS underlying cause is shock in general [40,41] and cardiogenic shock in particular [41] but neither they identify and explain the cause of cardiogenic deterioration, nor the devastating course of events, nor the lack of postmortem findings. Anaphylactic shock was also suggested but is unlikely as no evidences supporting an association of SIDS with allergy [42]. Undiagnosed sepsis was repeatedly suggested [17] but it lack solid evidence. Several researchers had proposed that SIDS common pathway is hypoxia [43], but hypoxia is a nonspecific universal end-stage finding in all deaths.

Several case reports and series had described diverse episodic events among which endocrine abnormalities such as thyroid, parathyroid and adrenal, etc. [44–46]. Metabolic crises were also suggested [47]. Other proposes included hyperthermia [48], hypothermia [49], Bradycardia in general and secondary to gastroesophageal reflux in particular [50]. None of the above is likely to explain the vast majority of SIDS.

Postmortem findings do exist but are inconclusive to identify the mechanism of death. Table 1 summarizes SIDS postmortem findings in several published series. The most considerable findings are: well inflated lungs, normal left ventricle, dilated right ventricle, empty bladder and liquid blood. There are nonspecific upper airway findings and intra thoracic petechia which are apparently different from suffocation [53,54]. Some of the inconclusive findings resemble or share similarity with findings seen in shock, sepsis and anaphylaxis [40–42].

The post mortem findings favor short devastating deterioration "fast death" on abrupt fatal event "immediate death". Immediate unexpected death due to an abrupt catastrophic event in adults is usually attributable to arrhythmia. SIDS post mortem findings are not supporting arrhythmia which is assumed to reveal nearly no post-mortem findings.

Other major abrupt catastrophic event in adults includes myocardial infarction, pulmonary embolism, extensive brain hemorrhage, and aortic catastrophe [60]. These catastrophic events would have been detected in post mortem at least in some cases.

Short devastating deterioration which leads to fast death in adults may also include in addition to the above: asphyxia, anaphylaxis, acidosis/alkalosis, oxygenation/deoxygenation and Shock. Metabolic or endocrine crises such as for example Addison crisis [46] are infrequent and are usually discernible on postmortem.

Oxygenation/deoxygenation events (e.g. methemoglobinmemia) is unlikely as it is extremely rare and usually discernible on postmortem.

Shock seems a considerable devastating deterioration cause, leading to fast death. Shock is a generalized impairment in cell level perfusion due to either a severe decline in CO or a severe decline in SVR or both.

Among the different types of shock, both obstructive shock and

Table 1
SIDS postmortem findings in several published series.

Organ/system	Autopsy findings	Authors' interpretation	
		Clinical significance	Indicative of either Immediate death or fast death
Frequent postmortem findings			
Heart	Diffuse focal anoxic muscle fiber necrosis, 70–100% of cases [14,43,51]	Nonspecific; frequently seen in shock in general and cardiogenic shock in particular	Fast death
	Right ventricle and atrium distention, nearly all cases [14]	Nonspecific; frequently seen in hypoxia and shock	Fast death
Lungs	Frothy excretion of fluid through nose or mouth, most cases [51]	Pulmonary congestion	Fast death
	Pulmonary congestion or pulmonary edema, > 50% of cases [2]	Nonspecific; frequently seen in hypoxia but also in heart failure, ARDS and shock	Fast death
	Well inflated lungs [51]	Nonspecific; excludes pulmonary morbidity or ventilatory disorder prior to death	Not indicative
Thoracic	Intrathoracic (pulmonary, thymus and epicardium) petechial hemorrhages, 68–100% of cases [2,51–54]	Nonspecific; frequently seen in acute death and hypoxia	Not indicative
Brain	Heavy brain, cerebral edema and congested brain structures, all brains studied [2,52]	Nonspecific; frequently seen in hypoxia (e.g., high altitude cerebral edema)	Fast death
Blood	Liquid blood, about 85% of cases [43,51,52]	Nonspecific; associated with acute death.	Not indicative
kidneys	Empty bladder [51]	Nonspecific; may be associated with impaired renal perfusion such as shock or with acute renal failure	Fast death
Thymus	Heavy thymus, all cases [43]	Surprising finding as acute stress is apparently associated with a small thymus (may be biased by lack of a previous comparable measurement)	Not indicative
Adrenal gland	Normal macroscopically; microscopically, moderate to massive congestion, 95% of cases [43]	Nonspecific; generalized congestion.	Fast death
Skin	Excessive sweating, ~50% of cases [51]	Typical in hyperthermia or shock (regardless of type)	Fast death
	Cyanosis of lips and nail beds, most cases [2]	Nonspecific; suggests chronic or long-lasting hypoxia	Fast death
Occasional postmortem findings			
Liver	Persistent hepatic erythropoiesis [51]	May be nonspecific and nonsignificant due to very high variability in hepatic erythropoiesis or biased by circumstances or associated with a premorbid condition (prematurity, chronic anemia, chronic hypoxia) or a risk factor or risk marker	Not indicative
Heart	Intramural coronary artery lesions [14]	Nonspecific	Fast death
Laboratory	Bacterial protein toxins [52]	Seen in toxemia/sepsis	Fast death
	Elevated cross-linked fibrin degradation [52]	Seen in toxemia/sepsis	Fast death
	Increased level of mast cell tryptase [42]	Seen in anaphylactic reaction	Fast death
	Increased lactate level [55]	Suggests hypoxia or shock	Fast death
	Fibrin degradation products (FDP) [56]	The explanation of fibrin degradation products (FDP) in SIDS is unknown given there are no findings of DIC or coagulation	Fast death
Upper respiratory tract	Mild or subacute inflammation, 44% of cases [51,52]	URI is frequent in most infants. The criteria for URI in post mortem are un-standardized. May be non-significant or coexisting finding	Not indicative
Larynx	Thickening of basement membrane – controversial [57]	Inconsistent, debated [58]	Not indicative
Brain	Brainstem gliosis [51]	May be associated with chronic hypoxia	Not indicative
	Quantitative brain-stem serotonin abnormalities [59]	Thought to be genetic abnormal malformation; may also be associated with immaturity of the neurological system. Such studies are infeasible in most settings and therefore lack validity	Not indicative

cardiogenic shock are discernible on comprehensive evaluation. Arrhythmic cardiogenic shock is unlikely, as noted above regarding arrhythmia. Hemorrhagic shock due to exsanguination can be excluded as it is discernible on postmortem. Hypovolemic shock due to dehydration can be excluded as it is not complying with the medical history and not supported by postmortem findings. Distributive (hyper-dynamic) shock is typically due to sepsis, anaphylaxis, or neurogenic shock. Septic or neurogenic shock are both identifiable on postmortem in most cases. Diagnosis of sepsis as the cause of death at autopsy can be challenging and it is possible that some cases macroscopic or histological infection foci may not be identified [61]. Hence, the claim that SIDS underlying cause is undiscovered sepsis cannot be entirely excluded episodically. However, it is unlikely that undiscovered sepsis explain the vast majority of SIDS cases. Moreover, we expect that diagnostic progress (such as PCR) would have increased the incidence ratio between diagnosed SUID and SIDS. Anaphylactic shock cannot be entirely excluded episodically, but no considerable association between SIDS and allergy has been presented [2]. There are rare causes of distributive shock such as endocrine and metabolic crisis in which the underlying cause is unlikely to remain occult in postmortem [46]. Non-septic distributive shock of undetermined cause had been previously described among adult intensive care unit patients [62].

The proposed potential stressors (hypoxia, hypercapnia, hyperthermia, infection, fever, inflammation etc.), share in common, a unified normal physiological response of decrease in SVR to facilitate compensatory increase in CO. The effect of vascular resistance and vasodilatation on CO is well known [63]. Under normal circumstances once the needs are met both SVR and CO are stabilized on a new steady state.

Hypoxia/hypercapnia induces a decrease in SVR via an increase in sympathetic tone and other dilating mechanisms, such as nitric oxide in order to increase CO to compensate for the impaired oxygen delivery [64].

Hyperthermia induces a compensatory decrease in SVR in order to activate the thermoregulation mechanism in general and increase cutaneous perfusion in particular. It may also be associated with an

increase in metabolic demands [65].

Fever, like infection and inflammation, is associated with an increase in metabolic demand that induce a decrease in SVR in order to facilitate an increased in CO to meet the metabolic needs [64,65].

What does the proposed hypothesis based on?

The hypothesis is based on the following facts: 1. The stressors (suggested by the triple risk model) share a unified compensatory physiological response of decrease in SVR to facilitate a compensatory increase in CO. 2. The cardiovascular/cardio-respiratory control of the vulnerable infant during a critical developmental period may be impaired. 3. A severe decrease in SVR is associated with hyper-dynamic state, high output failure and distributive shock (SVR collapse).

A multidisciplinary team of experts in diverse medical specialties (ENT, epidemiology, pathology, pediatric cardiology, pediatric endocrinology and pediatric intensive care) outlined four predefined challenging questions that any proposal regarding SIDS mechanism of death should answer:

1. How do the proposed triggers induce the proceedings leading to death?
2. What is the contribution of prone position?
3. How does the entire course from triggers to death go unnoticed and undetected?
4. Why does the mechanism of death remain obscure on postmortem examination?

The proposed hypothesis

We propose that non-septic hyper-dynamic shock (SVR collapse) may be SIDS mechanism of death.

The proposed proceedings are presented schematically in Fig. 1. The stressors according the triple risk model are the trigger that induces a normal physiological response of decreased SVR to facilitate a compensatory increase in CO. As was already noted, in normal circumstances once the needs are met both SVR and CO are stabilized on a new steady state.

The vulnerable infant during critical developmental period lacks a competent cardiovascular control [33]. It fails to stabilize SVR even if CO increases and comply with the needs. SVR consistently decreases in uncontrolled manner and accordingly CO increases far above the needs leading to hyper-dynamic state and high output heart failure. Neonate heart normally functions at near maximal capacity [66], hence increase in cardiac output and hyper-dynamic state may eventually reach maximal capacity which may risks hemodynamic stability and deteriorates toward hyper-dynamic shock. Under these circumstances multi organ failure and death are inevitable.

Infants increases CO mainly through increasing heart rate due to their limited capability to increase stroke volume. The increase in CO causes an increase in left ventricle end diastolic pressure which is reflected to the lungs causing increase in pulmonary pressure. The right ventricle (RV) hence has to cope both with volume load and increased after load which may lead to the RV dilation (as found in significant number of autopsies). The increase in stroke volume and tachycardia increase myocardial oxygen demand while supply is limited due to shortened diastole phase and increased end diastolic pressure, both decrease coronary flow. These processes may lead to myocardial cells hypoxia that may facilitate a secondary arrhythmia. Similarly myocardial depression is seen in sepsis which is also a hyper-dynamic state [67].

Shock limits kidney perfusion leading to acute renal failure which may explain empty bladder in postmortem [51]. Shock also decreases visceral perfusion leading to impaired bowel permeability which may explain previous reports on E-coli bacteremia [68].

It is well known that Sleep may depress cardio-respiratory/cardiovascular center [69].

As was previously suggested prone sleeping may impair circulatory

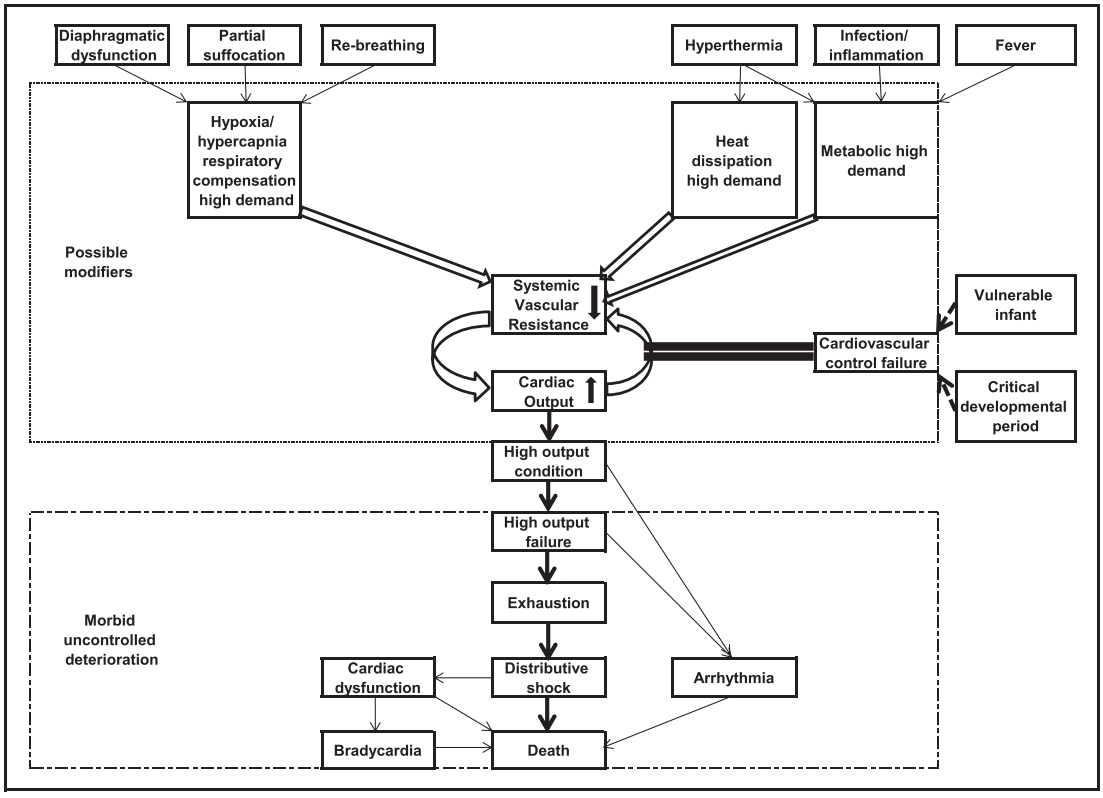

Fig. 1. Schematic Presentation of SIDS Proposed Unified Pathway Leading to Death.

control during sleep [10]. Waking-up may eliminate the devastating deterioration cascade entirely as there is no evidence of similar deterioration after wake-up.

Given the majority of SIDS occurs during night sleep in early morning [37], it may suggests sleep stage may play a worsening modifying effect (which was already suggested) [70].

The deteriorating course remains occult during sleep because the infant does not experience inconvenience during compensated hyperdynamic deterioration until exhaustion (decompensated stage). Infant of this age-range has a limited response capability by turning his head, restlessness or crying. While exhausted he may lose his response capability entirely.

During the entire course of hyper-dynamic deterioration the infant appearance is maintain normal, with preserved blood pressure, well palpable pulse, and noticeable respiration so inspection of the infant even just before death may raise no concern. SUID which eventually diagnosed as sepsis in postmortem is also remained undetected until death.

Hyper-dynamic shock is not expected to leave any specific diagnostic findings in post-mortem. SUID which eventually diagnosed as sepsis in postmortem manifests no conclusive findings related to the hyper-dynamic state per-se but rather findings related to infection and inflammation.

Hyper-dynamic state in general is difficult to diagnose [62]. High-output heart failure poses a diagnostic challenge as studies have found it is both under-estimated and under-diagnosed [71].

Conclusions

The proposed hypothesis covers the entire course from the trigger to death. It complies with the triple risk model and provides fair answers to the predefined questions.

We suggest that the hereby proposed hypothesis can be considered as an alternative to the existing speculations i.e. respiratory crises and arrhythmia. Nevertheless acute respiratory crisis or arrhythmias cannot be entirely excluded as SIDS potential mechanism of death.

Given the hypothesis is true what may further be done to prevent SIDS? The predominant paradigm of apnea as SIDS ultimate underlying cause misleads not only parents' insights but also professional caregivers. Hence it should be clarified that SIDS mechanism of death is unknown but unlikely to be apnea. Hence, doubtfully apnea monitors can be a preventive measure.

Supine sleeping is extremely important while prone sleeping should be entirely avoided (regardless what the underlying mechanism is) as a proven preventing intervention.

If high temperature is measured a hyperthermia rather than fever should also be considered given antipyretic medications are effective in fever but not in hyperthermia. Accordingly, the infant should be exposed, cooled and closely followed. Precautious should be given to prevent face proximity to bedding. Wake up the infant if a concern is raised and if infant sleep lasts too long.

The challenges of how to test the proposed hypothesis (either to prove or to reject) is extremely complex due to the exact same reasons the pathophysiology of SIDS syndrome is hard to delineate, as most victims are un-witnessed and post-mortem in most cases is inconclusive. Not only SIDS is too rare for prospective study but also clinical trials involving infants raise ethical and public concerns.

Awareness should be put on signs of hyper dynamic state. The hypothesis core parameters are SVR and CO, both of which may be measured directly through invasive measures which are neither justified nor feasible for healthy infants. Emerging non-invasive estimations methods for CO and SVR may be more appropriate but require sophisticated medical devices infeasible for monitoring healthy infants at home. Clinical trials enrolling hospitalized infants may be the only feasible option to monitor infants even though they are not necessarily representing healthy infants.

We suggest that physiological studies in animal model will be the first step targeting the stressors response of decreasing SVR and increasing CO. Simulating circulatory control failure in animal experiment will be the next challenge.

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Appendix A. Supplementary data

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