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Paroxysmal coughing, subdural and retinal bleeding: a computer modelling approach

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Paroxysmal coughing, subdural and retinal bleeding: a computer modelling approach

Unexplained subdural and retinal haemorrhages in an infant are commonly attributed to 'shaking', the mechanism of which is believed to be traumatic venous rupture. However, the haemorrhagic retinopathy reported as a result of Valsalva manoeuvres and the subdural bleeding that is a rare complication of pertussis together demonstrate that if a sustained rise in intrathoracic pressure is transmitted to cerebral and retinal vessels, it may result in bleeding, similar to that reported in inflicted injury. Such haemorrhages would be expected to occur whenever severe paroxysmal coughing were induced, whatever the cause. This study used a computer modelling approach to investigate feeding accidents as the trigger for bleeding. A dynamic circulatory model of a 3-month-old infant was induced to 'cough', and the response to changes in physiological variables monitored. It showed that coughing causes intracranial pressures to build up exponentially to approach a maximum, proportional to the amount of pressure the musculature of the thorax can produce, as venous return is impeded. They do not have time to become dangerous during individual coughs, as blood quickly returns after the cough is over, reestablishing normal pressures. Paroxysmal coughing, however, does not allow blood to return between coughs, with the result that very high luminal pressures may be generated, sufficient to damage veins. A history of coughing, vomiting or choking is not uncommon in otherwise normal infants with retinal and subdural bleeding. Our findings suggest that paroxysmal coughing could account for such bleeding in some cases.

Keywords: paroxysmal coughing, retinal haemorrhage, subdural haemorrhage

Introduction

The pathogenesis of infantile retinal and subdural bleeding is as yet unresolved, although most physicians remain convinced that 'shaking' is the principal cause, once a number of rare alternative explanations have been excluded. In such a scenario, vigorous to-and-fro movements of the brain inside the skull rupture bridging veins – a mechanism extrapolated from the acute subdural haematomas that occur in accidental trauma in older children and adults. However, recent biomechanical work strongly suggests that shaking at levels known to cause structural brain damage [1,2] cannot rupture bridging veins without first causing severe structural neck injury and traumatic brain damage [3–5]. Impact to the head is a much more likely cause of subdural haemorrhage [3,6], because it results in greater movement of the brain and distorts the immature skull [7,8]. Nevertheless, despite this evidence, the accepted medical opinion is still that unexplained subdural and retinal bleeding in an infant showing no signs of impact are most likely to be due to 'shaking'.

Subdural and retinal haemorrhages are not diagnostic of abusive injury, neither alone nor in combination, and there are clearly several mechanisms by which they may occur. They have been reported in accidental trauma [9]. They have also been documented to occur in a range of

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clinical situations in which trauma is not involved, in which one or more of a number of different factors including coagulopathy, cerebral atrophy, extreme central venous congestion, raised intracranial pressure and profound hypoxia may be aetiologically significant, according to the clinical situation [10,11]. Both subdural and retinal bleeding also occur after a proportion of normal deliveries, in neonates and in premature babies [12–14] though no study has ever attempted to assess whether both may be present together in this particular cohort. Of particular interest is how otherwise normal young children may present with subdural and retinal bleeding, without evidence of any of the above factors, if not from being 'shaken'.

On anatomical and physiological grounds alone, subdural and retinal bleeding could occur when raised intrathoracic or intra-abdominal pressure is transmitted to the intracranial circulation [15]. The olfactory and visual systems evolved as extensions of the brain and so derive their circulation from intracranial vessels. Ethmoidal arteries, the retinal arteries, and the arteries to periorbital skin are all branches of the ophthalmic artery, which arises from the internal carotid; the corresponding veins drain into the cerebral venous system. The result is that luminal pressures in retinal and nasal vessels follow those within the brain. Raised pressure within the chest and abdomen in Valsalva manoeuvres restricts blood flow back to the heart and increases the pressure within retinal veins, resulting in retinal bleeding [16–18]. The actual incidence of such an occurrence is unknown, because haemorrhages sparing the macula may be asymptomatic, and only severe cases get reported. Whether there is simultaneous leakage of subdural blood is also unknown, because all the recorded cases of Valsalva retinopathy are of course adult, and the situation will be different in a fused skull, where vessels are unable to distend to the same extent as in infants. Patients with very thin subdural haematomas do not have symptoms of an acute intracranial bleed and so would not be investigated, but the same mechanism – transmission of raised intrathoracic pressure to the brain – has been implicated as a cause of subdural bleeding [19,20]. Indeed, having studied the structure of cerebral bridging veins in detail, Yamashima and Friede concluded that 'not only sudden acceleration or deceleration of the head but also sudden increases in venous pressure can lead to an augmentation of tension especially at the subdural portion of the bridging veins, thus inducing subdural bleeding' [21].

One condition in which raised pressure in the system leads to a whole range of mechanical complications, including intracranial bleeding, epistaxis, conjunctival and periorbital petechiae, is pertussis. Bordetella pertussis attaches to cilia, disabling them, and so allowing mucus to accumulate in the airways. The resulting irritation causes powerful paroxysms of coughing, with marked swings in intravascular pressure. Serious secondary complications such as intracranial haemorrhage were regularly reported when whooping cough was more common than it is today. The emphasis in the early literature is that meningeal bleeding, particularly in the subdural space, was the most usual type of intracranial haemorrhage [22–25]. Full *post mortem* reports that include a neuropathological examination are unusual, but a detailed early description of a child who died of pneumonia following severe pertussis documented bilateral subdural bleeding, in addition to cortical venous thrombosis and venous infarction [26] and though exceedingly rare, subdural bleeding remains a recognized sequela of the paroxysmal coughing of pertussis today [20,27,28], with or without brain swelling. Subconjunctival haemorrhages are regularly reported in severe cases of pertussis, and although retinal bleeding probably also occurs there are again no reports in the literature documenting fundal or histological examinations of the eye in pertussis patients who have had subdural haemorrhage.

In a significant proportion of cases in which abuse is alleged because retinal and subdural bleeding have been found, there is a preceding history of aspiration of feed, choking or vomiting, with paroxysmal coughing. Could such a history be aetiologically relevant? Investigation of the pathophysiology of cough-related injury is difficult: the rarity of infantile subdural and retinal bleeding precludes observational studies, and infant experimentation is impossible. Variations between species render animal models unreliable. We have adopted a computer modelling approach, using a model of an infant which can be induced to 'cough' in a variety of patterns, and in which the resulting vascular pressures can be monitored and compared with those thought sufficient to produce paroxysmal cough injury (PCI) [15].

Hypothesis

That paroxysms of coughing from any cause, including from aspiration of feed or vomit, can generate sufficient rise in vascular luminal pressure to cause PCI, a pattern of

intracranial and intraocular bleeding identical to that of the 'shaken baby syndrome'.

Methods

CALEB is a mathematical software model of a 3-month-old infant constructed from approximately 600 physiological variables, each variable being based on several references taken from the literature that agree among themselves. Written in the language Borland Turbo C, the main program occupies about 430 kilobytes of computer space, and is in essence a database of organ behaviours converted into mathematical forms which can be linked to allow interactions to be studied. Simple mathematical and logical functions interrelate a series of subprograms, operating in turn to recalculate changes in all the variables every 5 ms of represented time. The subprograms that make up the model deal with different physiological aspects such as circulation, respiration, blood gases and oxygen supply to various organs (Figure 1). They interact as they would *in vivo*, enabling the investigator to modify one or more of the physiological parameters and monitor the results.

Our infant model 'CALEB' was originally developed from the feto-placental model 'Fetal Charlotte', which has been described in detail elsewhere [29]. Fetal Charlotte has been applied to the study of gestational problems where there would be ethical and experimental restrictions on research – for example, in the investigation of fetal pulmonary flow in hypoxia, or the twin-to-twin transfusion syndrome [30–33]. The studies have shown such a model to be a useful tool, capable of yielding clinically relevant and verifiable information [34]. However, in order to use models of this complexity, validation has to be a continuous process during development, with each stage of the build validated before proceeding to the next. The example that best demonstrates the validity of the volume/pressure capabilities of CALEB in relation to the present study is the jugular flow pattern at the start of Figure 2 (f). This is the jugular venous pulse, which provides information about haemodynamic changes in the right side of the heart, including abnormalities of right ventricular and atrial filling. The resting pattern generated by CALEB is very closely comparable to that produced by normal human jugular flow, as detected by ultrasound

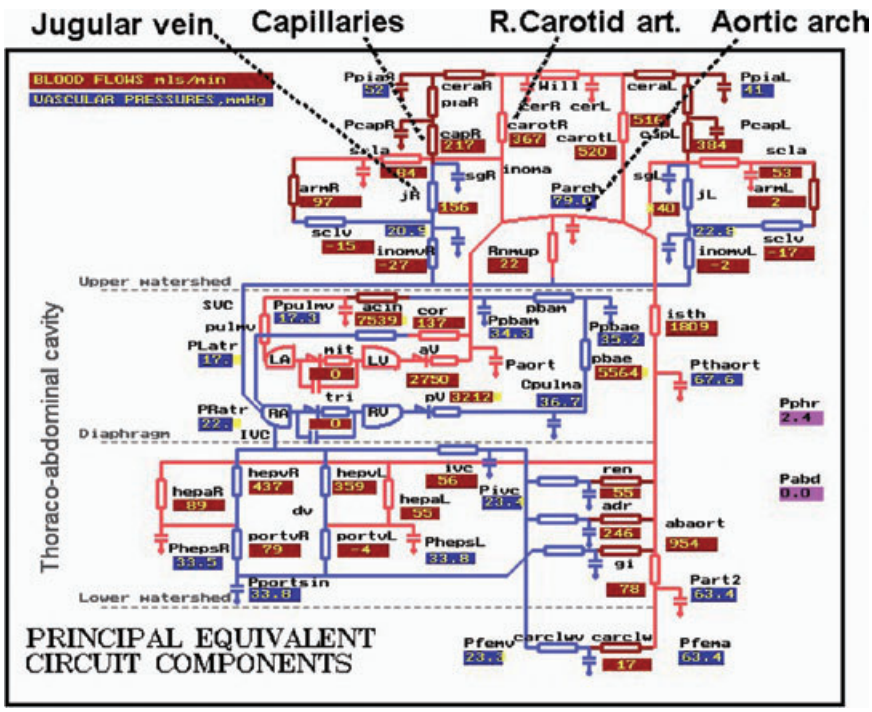

Figure 1. The circulatory subprogram in CALEB: a screen capture shows the equivalent electrical circuit, or blood flow map, used for computation. The short parallel lines represent the vessel wall compliances, while the open rectangles represent the resistance to flow along each pathway. The 'watershed' lines indicate the boundaries between which cough pressure becomes superimposed on all tissue within the body when coughs are introduced. The region relevant to this study lies above the upper watershed line.

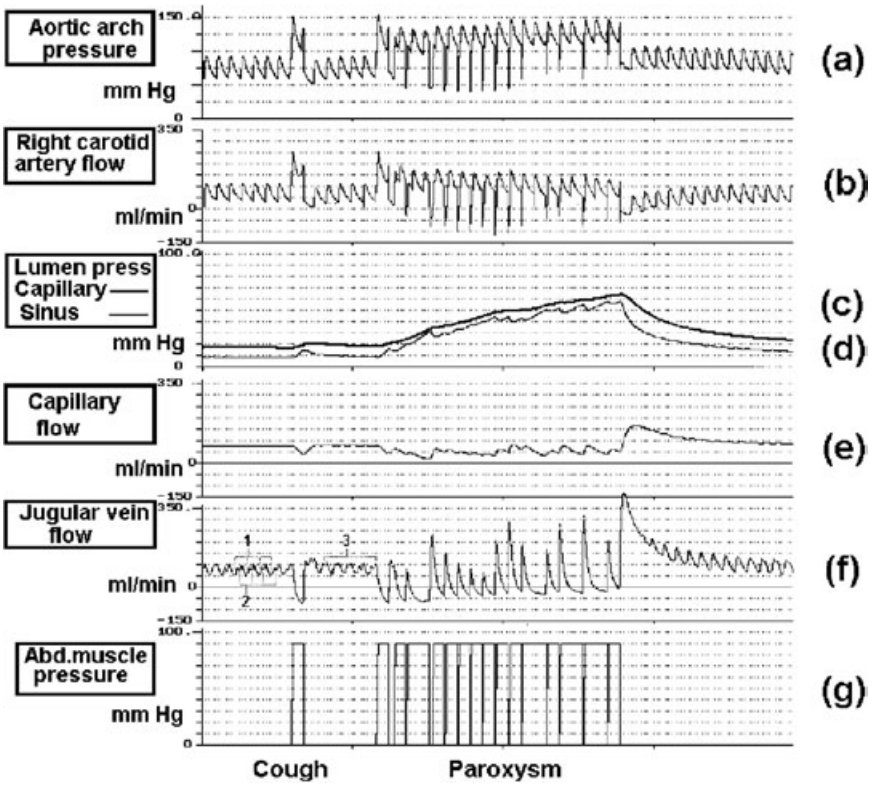

Figure 2. Polygraph display during a single cough, followed by a paroxysm. Abdominal pressure (**g**) produced by abdominal muscles during coughs raises aortic arch pressure (**a**) causing a surge of carotid artery flow (**b**) into the skull, raising brain capillary perfusion pressure (**c**). Simultaneously, raised superior vena cava pressure produces reverse jugular venous flow (**f**) which adds to brain outflow to produce a rise in brain sinus pressures (**d**). The pressure difference driving blood through the capillaries is the distance between traces (**c**) and (**d**), seen in trace (**e**). The capillary blood flow is briefly reduced in single coughs, but this reduction is sustained during a paroxysm. Accumulated blood cannot escape during a paroxysm, and excessive brain perfusion (**c**) and venous (**d**) pressures result. The numbers 1, 2 & 3 on trace (**f**) refer to significant events influencing the normal shape of the jugular venous flow waveform (see text).

or derived indirectly from pressure waveforms. Flow increases as atrial pressure falls when blood drains through the tricuspid valve in the early phase of ventricular filling (1), reaching a maximum during right ventricular systole, but interrupted briefly by atrial contraction pressure (2). The significance of the changing pattern following a single cough (3) is that the rise in venous pressure during inhibition of venous return dominates ventricular refilling, and the atrial pulse only becomes visible again once the 'backlog' has been cleared. In summary, the trace demonstrates that the model has adequate pressure/volume resolution to indicate events in the cerebral venous circulation resulting from a paroxysm of coughing, within the time frame of the study. (Note that as used here CALEB can only deal with the acute stage of an insult: it does not incorporate factors that would enable us to investigate longer response times.)

For reasons of space we are only able to describe the features of CALEB that are relevant to the present study – namely, the circulatory and respiratory subprograms. The circulatory subprogram is based on the principle that the flow of blood and the flow of electricity follow similar laws: movement of blood results from pressure differences measured in mmHg, and electricity flows under electrical pressure (volts). The flow of blood (ml/min) corresponds to electric current (amps). By defining corresponding analogue quantities, mathematical techniques developed for electrical problems can be transferred to the circulation, and complex relationships can be investigated using an electrical equivalent circuit. Figure 1 shows one of its displays in the form of an electrical equivalent circuit of the principal organs, which represents the infant as a network of interconnected blood vessels of appropriate flow resistance and compliance. Flow to each side of the brain is sep-

arately represented, but hemispheres, cerebellum and brainstem are treated as 'lumped' for each side. Similarly the main arterial supply to the brain is via carotids and vertebral arteries, but for the purposes of total arterial volume and flow on each side their contributions are combined in the components carotL and carotR. The particular region relevant to this study is the brain circulation representation from aortic arch to right atrium (carotR&L-ceraR&L-piaR&L-capR&L-jR&L-inomvR&L-RA). CALEB adopts the convention that cerebral arteries (ceraR&L) are myogenic pressure regulators, and that pial arteries (piaR&L) and deep arterioles are metabolically sensitive local flow regulators. In the brain the pressure drop is proportionately larger on the arterial side, and smaller on the venous side than in most somatic tissues. For that reason the resistances of the venules, veins and sinuses are merged into the capillary figures, and the sinus pressure shown is that appearing at the entry to the jugular veins. During coughs the jugular and vertebral veins are subject to additional intrathoracic pressure, their combined flow being represented mathematically by jL and jR.

The respiratory subprogram in CALEB has a brainstem model [35] which controls air flow resistance through a larynx, and then calculates the resulting air flow down the respiratory tract to alveolar diffusion level. A diaphragm and abdominal muscles are also included. Systemic circulation time is significantly longer than a single paroxysmal coughing fit, which means that total body oxygen content will not have time to change significantly, and the resistance of blood gas sensitive arterioles (e.g. piaR&L) remains constant during a paroxysm, so for this study the only relevant feature is the respiratory musculature. Coughing in single or paroxysmal patterns is simulated by injecting one or more signals into the abdominal muscle control system as simple square wave drives from the keyboard.

The model can be halted at any time and pressures (blue boxes) and flows (red boxes) read off the screen. Sets of variables can be selected for alternative polygraphic displays, one of which is shown in Figure 2.

Results

The principal results are summarized in Figure 2, which is taken from the model's polygraph display during a single cough (*left*), and a cough paroxysm (*right*). For simplicity only the values for the right side of the brain are shown. When the abdominal muscles contract in a cough all pressures within the body, including the aortic arch (a), are raised above those in head and limbs [15]. This causes blood to be expelled to the head and neck, raising vascular pressures in those sites. Vascular beds take time to accumulate additional volumes so brain perfusion (c) and venous (d) pressures do not reach excessive pressures in single coughs.

Cerebral venous volume increases both by accumulation of blood flowing out of the brain, which cannot return to the heart against the reverse gradient, and by reverse leakage (f) through the relatively inefficient jugular valves (a 20:1 reverse to forward flow resistance was set in this example), for the duration of the cough. The rise in venous sinus pressure (d) was only about 12 mmHg in the duration set for a single cough.

In paroxysmal coughing, however, blood is driven into the head by the high cough pressures, with only brief intervals in which blood can return to the heart, under the pressure that has developed in the venous system. In parallel, the vertebral venous plexus is under pressure in the thoracic and abdominal regions, and so is largely unavailable to buffer rises in cerebral venous pressure. The display shows that cerebral venous pressure (d) rises by about 50 mmHg above baseline, followed by a rapid recovery to normal volumes and pressures after each paroxysm. Changes in blood pO_2 do occur but in a single paroxysm the fall in saturation is small, and is not a factor in Figure 2. Clinically, continuous repetition of such paroxysms in choking may well superimpose hypoxic damage as it does in pertussis, but that is beyond the scope of this model and study, which is concerned with the acute mechanical aspects of injury.

Discussion

Computer modelling offers a way of altering physiological variables in order to test a hypothesis, in situations in which human experiments would be impossible or unethical. In the present instance the behaviour of our model has supported clinical observations, showing that the conditions necessary for subdural and retinal bleeding do occur in paroxysmal coughing, although it cannot prove that the bleeding is necessarily or even actually present clinically. Despite the model being numeric, the numbers must not be taken literally, as they are merely the calculations for values taken from the literature; it is the trends

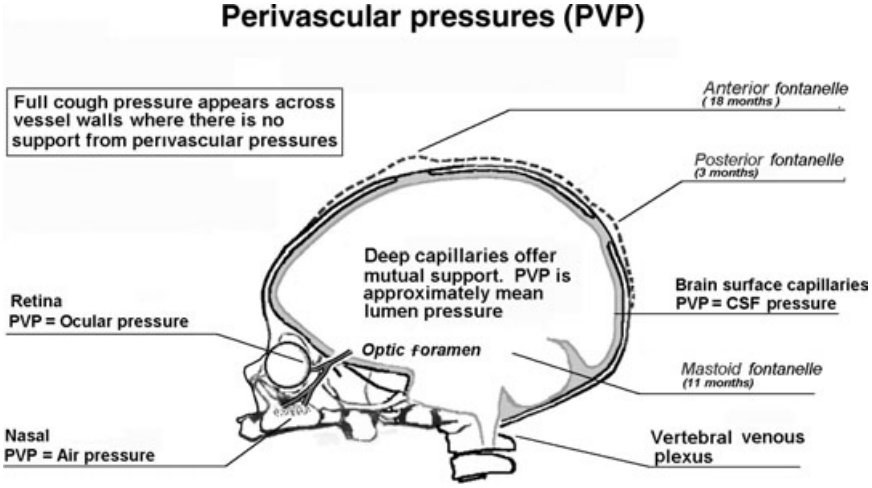

Figure 3. Sites vulnerable to paroxysmal cough injury. Ocular pressures surrounding retinal veins do not change significantly when intraluminal pressures are raised, so the vessels will receive no support and are likely to bleed. Similarly, as intracranial pressure rises during a paroxysm of coughing the infant skull can expand. This permits intravascular pressure to rise further. Vessels on the surface of the brain find themselves relatively unsupported compared with those running through the brain parenchyma: veins in the subarachnoid space are surrounded by cerebrospinal fluid (CSF) pressure which initially is unsupportive, while the dural border layer is inadequate to support subdural veins (see text). As a result, meningeal rather than parenchymal haemorrhage occurs. In contrast to traumatic venous damage, bleeding from raised intravascular pressure may occur at the base of the brain as well as over the hemispheres. Because the thoracic and abdominal segments of the vertebral venous plexus are pressurized during a paroxysm of coughing, leakage of blood may well also occur in the cervical region.

shown by the model that are important. They demonstrate clearly that dangerous rises in intravascular pressures, which may exceed the failure threshold of intracranial veins, are generated by a prolonged bout of coughing. The effects would be expected to be greater on the venous side because the proportionate rise in pressure is larger.

Paroxysmal coughs are in effect very high pressure Valsalva manoeuvres – indeed, if reflex laryngeal closure takes precedence, coughs will be replaced by Valsalvas, which have a well-established association with retinal haemorrhage. In paroxysmal coughing the cough pressures are transmitted to the lumina of all vessels. Within the body interstitial pressures are equally raised, so that vessel walls are supported against rises in luminal pressure, but inside the orbits, nose and infant skull such support is largely lacking, leaving vessel walls exposed to the full lumen pressure and so vulnerable to rupture (Figure 3).

Blood vessel failure

The robust construction of arterial and arteriolar walls means that they can withstand high pressures and are unlikely to leak if blood pressure is raised, though the arterioles may lose their ability to protect capillaries. Studies have shown that sudden acute hypertension damages the smooth muscle in cat pial arterioles, leaving them locally dilated like a 'sausage-string'. Recovery of any pressure regulatory function takes several hours, with the result that capillaries find themselves exposed to abnormally high pressures [36–38]. In conditions such as pertussis, or where there is laryngeal spasm after aspiration, hypoxia-induced cerebral arteriolar dilatation will exacerbate this situation.

No research specifically addressing the question of stress failure of intracranial veins appears to have been reported in the literature. However, experimental studies of acutely raised venous pressure have shown that breakdown of the blood–brain barrier (BBB) is the initial event, with haemorrhage occurring at pressures approximately twice those necessary to disrupt the BBB. Yoshimoto *et al.* raised local venous pressure by occluding a cortical vein in the adult dog. Increasing amounts of oedema were recorded at pressures above 7.7 ± 3.2 mmHg, with parenchymal haemorrhage occurring at 16.4 ± 5 mmHg [39]. Mayhan and Heistad's studies of rat pial venous pressure and BBB disruption during acute arterial hypertension and superior vena cava occlusion found that venules dilated markedly in both experimental situations, and

became increasingly leaky. By means of labelled dextran tracers the authors were able to demonstrate that venules and veins, not capillaries, were the primary sites of BBB disruption [40,41].

Very high intracranial pressures may be generated even by single coughs. According to Lumb, the superimposition of abdominal muscle pressures on normal working pressures during a cough can transiently drive cerebrospinal fluid, thoracic, and arterial pressures up to 300 mmHg in adults [42]. This is confirmed by a study of gastric pressure (a measure of abdominal muscle effort), in which Man *et al.* obtained single cough peak pressures of 156 ± 30 mmHg in males and 120.4 ± 24.8 mmHg in females [43] – which when added to normal arterial pressures give results of the same order. In the only similar study found relating to infants, Perlman showed that premature infants on ventilators produced high transient arterial pressures when they coughed, and that paralysing them to prevent coughing eliminated intraventricular haemorrhages [44]. It may seem surprising that neonates may produce sufficiently high pressures to cause bleeding, but the explanation is geometrical. Although the abdomen is strictly neither a thin-walled tube nor a sphere, Laplace's relationship (lumen pressure is proportional to wall tension/radius) is applicable to the ratio of pressures in similar hollow structures, and because the infant's abdomen is so much smaller than that of an adult, proportionately less abdominal wall tension would be required to produce the same pressure. As Yoshimoto *et al.* documented venous leakage at a pressure of only 16.4 ± 5 mmHg in dogs, and we have shown rises of the order of 50 mmHg above baseline in paroxysms, it seems highly likely that cough pressures in infants would be sufficient to produce such bleeding.

Bridging veins within the dura are supported by a network of collagen, and in the subarachnoid space are wrapped around by trabeculae containing collagen fibres [21,45]. Between the dura and arachnoid there is a 'border layer', continuous with both [45,46], and acting as a bonding layer between them. It contains no collagen, and is so mechanically weak that for many years its existence was not realized, being spoken of as a 'virtual' subdural space. Electron microscopy has, however, shown that the junction is an identifiable layer of relatively weakly attached cells [46,47] which provides support under normal conditions but cannot protect against excessive intraluminal pressure. The fact that this is not only the most unsupported segment of the bridging vein, but also the site at which the thickness of its wall is most variable (often as thin as 10 μ, according to Yamashima and Friede [21]), explains why this is the point at which bridging veins would give way under excessively high venous pressures and leak or burst, causing subdural bleeding (Figure 4).

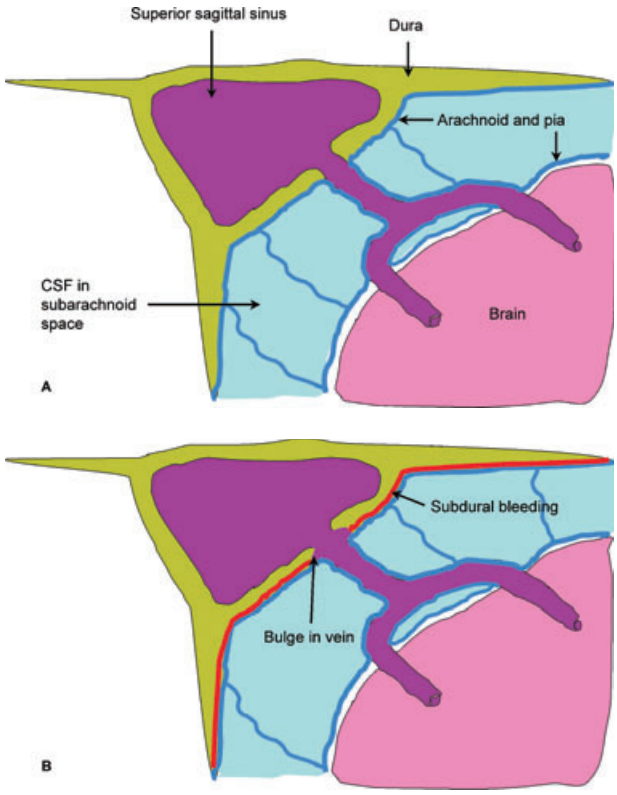

Figure 4. (**A**) Normal meningeal anatomy. Bridging veins draining to sinuses within the dura receive support from surrounding tissue as they pass through the arachnoid and dura, but the junction between the two layers is very weak, and allows the veins to distend and leak. (**B**) Thin-film subdural bleeding caused by paroxysmal coughing. (Diagrams reproduced by kind permission of Prof. RO Weller). CSF, cerebrospinal fluid.

Cough trigger mechanisms and PCI

Cineradiographic studies of swallowing in bottle-fed lambs and human infants reveal that in addition to synchronization of pharyngeal, laryngeal, and oesophageal actions, complex movements of the tongue are required to ingest liquid feed successfully [48,49]. Any infant having difficulty acquiring feeding skills will be at risk of dysphagic PCI, and as solid and semisolid feeds require further skill

development, the period of weaning will present further risks.

Paroxysmal coughing or choking resulting from inhalation of feed or vomit results in powerful expiratory efforts. While such coughing may on its own pose the threat of PCI, inhalation of feed or vomit past the glottis may aggravate the situation by stimulating the persistent laryngeal closure reflex. Amateur cardiopulmonary resuscitation, and even attempts at intubation by trained personnel may be impossible until laryngospasm relaxes, resulting in prolonged severe hypoxaemia. In summary, in PCI factors such as secondary hypoxia and dangerous rises in intrathoracic pressure will complicate the clinical picture and contribute to the ultimate pathology.

Conclusion

The results of this study show clearly that the conditions for subdural bleeding may occur in an otherwise normal infant, in the absence of trauma, where paroxysmal coughing or expiration against a closed larynx last long enough for excessive pressures to develop. Subdural bleeding would be accompanied by retinal bleeding, because central venous pressure in the eye is the same as venous sinus pressure in the brain. Epistaxis could also occur. The model has explained retinal and subdural bleeding in Valsalva manoeuvres and in whooping cough, reminding us that such haemorrhages are not pathognomonic of shaking. Many cases of alleged child abuse in which there are no other injuries present with a clear history of feeding difficulties or choking, with coughing. The history itself is usually ignored. Reports of blood or blood-stained fluid round the nose may even give rise to allegations of suffocation. The mechanism we have outlined here would be relevant to both fatal and non-fatal cases, and investigation of an infant who had suffered PCI would fail to reveal any of the recognized conditions predisposing to subdural bleeding. In the light of this, we suggest that it is not justifiable to use subdural and retinal haemorrhages as criteria to conclude that abuse has taken place, even if other known causes of such bleeding have been excluded. The fact that small-volume subdural bleeding may result from generalized leakage through congested veins or capillaries as a result of raised intravascular pressure, rather than from direct traumatic damage to vessels, does not exclude abuse. It does, however, mean that establishing the pathogenesis of the clinical findings in such cases may be critical.

Acknowledgement

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Competing interests

JFG has given evidence in Court in cases of alleged child abuse, both for the prosecution and the defence. There are no other competing interests.

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