An Argument for Neurogenic Induced Severe Apnea as the Potential Initiating Event in Sudden Death or Cardiopulmonary Arrest Following SAH. An Experimental Study and Review of the Literature.

Gavin W. Britz, Eugene V. Golanov.

Department of Neurosurgery
The Houston Methodist Hospital,
Houston, Texas.
DISCLOSURE STATEMENT

I or my spouse/partner or my co-author’s financial and organizational relationships DO NOT have any financial or organizational relationships with commercial interests or other entities. I hereby certify that to the best of my knowledge, no aspect of my or my co-authors’ s current personal or professional circumstances places me or my co-authors in the position of having a conflict of interest with my duties, responsibilities and exercise of independent judgement as an Officer, Member of the Board of Directors, Nominee for Office, Educational Presenter and/or a representative of AANS/NREF/NPA.
Introduction.

Aneurysmal Subarachnoid hemorrhage (SAH) is still associated with a significant mortality and morbidity. While numerous studies addressed cellular and molecular damages following SAH, relatively little is known of the early events following aneurysm rupture. It is well known that an Aneurysmal SAH is commonly associated with a cardiopulmonary arrest. In the vast majority of the cases of SAH, the first few minutes after the ictus go unwitnessed or unwitnessed by medical personal, and therefore the true incidence of either a transient loss of consciousness or a short term apneic spell is truly unknown. Therefore, the known data support the fact that the underlying mechanism of a cardiopulmonary arrest or sudden death following SAH is not well understood and has not been proven. We hypothesize that a neurogenic induced severe apnea is the precipitating event in a brief loss of consciousness, sudden death or cardiopulmonary arrest following an SAH. In addition, the associated hypoxia would aggravate brain injury in those that survive the initial event.
Methods.

Studies were performed in 123 10-14 weeks old male C56BL/6J mice (Jackson Labs). Animals were anesthetized with Isoflurane, and SAH was induced using monofilament perforation of the Willis circle. The hemorrhage was scored using modified grading scale developed by Sugawara et al., (2008) as it correlates with the neurological status. ECG was recorded between right and left front paws. Signals were digitized, and respiratory movements were derived using band-pass filter from 0.5 to 2.5 Hz applied to the ECG signal. To measure intracranial pressure, pressure catheter, 0.33 mm diameter, was introduced to 2.0 mm depth. Regional cerebral blood flow (rCBF) was recorded using needle probe (1.5 mm diameter) placed over the intact skull over the parietal cortex on the side of perforation. Arterial pressure (AP) was monitored through the catheter introduced in the femoral artery. For intraventricular injection, capsazepine (Czp) was dissolved in 20% dimethyl sulfoxide (DMSO) and diluted to 1 µg/2.5 µl of 2% DMSO in artificial cerebrospinal fluid (aCSF)); 2% DMSO in aCSF was used as control. Injection was performed using stainless still tubing introduced through the small burr whole at -1 mm from bregma, 1.5 mm lateral from midline at the depth of 2 mm using micropump. Solutions were prepared ex tempore.
Results.

In all animals (n=123) heart (HR) and respiratory rate (RR) were recorded. In addition, in 5 animals we also explored changes in AP, rCBF and intracranial pressure (ICP) following the SAH. In these animals following the perforation within the first minute ipsilateral rCBF dropped by 80±15% (p<0.001) (Fig. 1A), mean AP decreased by 13±2 % (from 97±8 to 82±11 mmHg, p= .39) (Fig. 1B), ICP transiently increased by 102±12 % (from 6±2 to 24±5 mmHg, p= .05) (Fig. 1C), cerebral perfusion pressure decreased by 40±7% (from 82±2 to 49±4 mmHg, p= .02) (Fig. 1D, and HR increased by 6±3% (from 455±23 to 484±35 beats/min, p= .05) (Fig. 1E).

Immediately following the perforation, 95% of all animals (117 out of 123) demonstrated dramatic decrease in RR by 69±12%, from 0.9±0.1 to 0.2±0.2 breaths/sec, p< .001, which progressed to apnea in 73% of cases. The first inspiration following perforation occurred in 30±16.8 sec (Fig. 1F, Fig. 2). In 26% of animals, apneic period lasted over 1 minute. In animals, which experienced complete respiratory arrest for over 2 minutes, mechanical chest stimulation was required for “resuscitation”. Once the spontaneous respiration was reinstated, animals regained regular RR. This simple maneuver decreased
mortality from 46% to 7%. No correlation between the SAH score and RR suppression was observed (Spearman correlation -0.55, p= .33). No changes in RR or any other parameters were observed in animals with “sham” perforation. The lack of correlation between the size of hemorrhage and very short latency to apnea suggests the neurogenic origin of the phenomenon.

Dura mater is innervated by the nerve fibers endowed with transient receptor potential vanilloid type 1 (TRPV1) receptors. To explore possible involvement of TRPV1, one hour before the perforation capsazepine (Czp), blocker of TRPV1 channels (2 μg in 5 μl of 2% DMSO in aCSF), was injected intraventricularly. Czp failed to modify baseline parameters and acute autonomic responses to SAH.

Data reveal severe respiratory abnormalities in response to SAH, while ECG remained unperturbed. Very short latency of the apneic response and its independence from the size of the hemorrhage strongly suggest neurogenic origin of apnea. Failure of Czp, to modify respiratory and other autonomic responses to SAH evidences against involvement of TRPV1 channels. SAH.
Fig. 1. Changes in physiological parameters following circle of Willis perforation in mice.

Acute changes (delta percent of the baseline) in major physiological parameters within first five minutes after the perforation: A. cerebral blood flow; B. mean arterial pressure; C. intracranial pressure; D. cerebral perfusion pressure; E. heart rate; F. respiration rate. Mean value of respective parameter is represented by red trace. Blue cloud represents standard error of the mean. Green trace represents changes of the respective parameter in sham animals. Green vertical line indicates moment of perforation. Purple vertical line indicates end of the initial 5 minutes of observation followed by the dynamic status of the parameter one hour after the perforation. Note the acute drop in respiration rate immediately following the circle of Willis perforation.
Fig. 2. Simultaneous recording of ECG (upper trace) and respiratory movements (lower trace) immediately following the perforation of the circle of Willis. Note the abrupt apneic response while ECG remains stable. Time indicates minutes:seconds.
Discussion.

Respiratory arrest may occur for a variety of reasons. Regardless of the cause, it is a life-threatening situation which requires immediate management. When a patient goes into respiratory arrest, the associated rapidly developing hypoxia may result in anoxic brain injury or cardiac arrest within minutes if not promptly treated.

The underlying mechanism or initiating event of the recently described brief loss of consciousness or well described cardiopulmonary arrest is not understood. The lack of correlation between the spread of hemorrhage and the very short latency to apnea suggests the neurogenic, reflexive origin of the phenomenon.

Dura mater is richly innervated by afferent nerves originating in the ipsilateral trigeminal ganglion. Stimulation of trigeminally innervated structures, including dura mater is capable of triggering so-called trigemino-cardiac reflex, which includes apnea. Mice trigeminal afferent neurons are endowed with TRPV1 receptors participating in inflammatory pain, hyperalgesia, and hyperthermia. However, failure of capsazepine to prevent apnea suggests that TRPV1 channels do not play a leading role in the apneic response to acute SAH.
Summary points.

Aneurysmal SAH is associated with a significant mortality and morbidity and in particularly in the ultra-early outcome following an SAH. To improve the outcome, we must first understand the mechanisms involved that contribute to the poor outcome in the ultra-early time period following an SAH.

Our data reveal that:

- Early severe respiratory abnormalities in response to SAH could be initiating event of the high mortality following SAH;
- The duration of SAH-induced acute apnea may affect short- and long-term outcome of this catastrophic event;
- Data suggest that neurogenically induced severe apnea may be part of the described in patients trigeminocardial reflex
- TRV1 receptors do not seem to be involved in the acute neurogenic apneic response to SAH.