

HIGHLIGHTED TOPIC | *A Physiological Systems Approach to Human and Mammalian Thermoregulation*

Respiratory responses to cold water immersion: neural pathways, interactions, and clinical consequences awake and asleep

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Datta, Avijit, and Michael Tipton. Respiratory responses to cold water immersion: neural pathways, interactions, and clinical consequences awake and asleep. *J Appl Physiol* 100: 2057–2064, 2006; doi:10.1152/jappphysiol.01201.2005.—The ventilatory responses to immersion and changes in temperature are reviewed. A fall in skin temperature elicits a powerful cardiorespiratory response, termed “cold shock,” comprising an initial gasp, hypertension, and hyperventilation despite a profound hypocapnia. The physiology and neural pathways of this are examined with data from original studies. The respiratory responses to skin cooling override both conscious and other autonomic respiratory controls and may act as a precursor to drowning. There is emerging evidence that the combination of the reestablishment of respiratory rhythm following apnea, hypoxemia, and coincident sympathetic nervous and cyclic vagal stimulation appears to be an arrhythmogenic trigger. The potential clinical implications of this during wakefulness and sleep are discussed in relation to sudden death during immersion, underwater birth, and sleep apnea. A drop in deep body temperature leads to a slowing of respiration, which is more profound than the reduced metabolic demand seen with hypothermia, leading to hypercapnia and hypoxia. The control of respiration is abnormal during hypothermia, and correction of the hypoxia by inhalation of oxygen may lead to a further depression of ventilation and even respiratory arrest. The immediate care of patients with hypothermia needs to take these factors into account to maximize the chances of a favorable outcome for the rescued casualty.

cold shock; drowning; underwater birth; sleep apnea

THE VENTILATORY RESPONSE TO immersion is not purely of academic interest; it can be the precursor of drowning, a major cause of global mortality. There are 500,000 drowning deaths every year worldwide (59), and drowning is the second leading cause of accidental death in the European Union and the United States (79). In 2001, there were 3,281 unintentional drownings in the United States, averaging nine people per day. This does not include drownings in boating-related incidents (5). For every child who drowns, three receive emergency department care for nonfatal submersion injuries. More than 40% of these children require hospitalization (5). Nonfatal incidents can cause brain damage that result in long-term disabilities ranging from memory problems and learning disabilities to the permanent loss of basic functioning (i.e., persistent vegetative state). Among children aged 1–4 yr, most drownings occur in residential swimming pools (8). Most young children who drowned in pools were last seen in the home, had been out of sight less than 5 min, and were in the care of one or both

parents at the time (60). Thus any factors which may modify the mortality and morbidity of drowning would have a major impact on global child health.

For those who survive the hazardous initial responses to immersion and superficial cooling, hypothermia becomes an increasing risk, particularly for those in remote areas, or when search and rescue capabilities are limited, such as at times of conflict.

In this paper we focus on the ventilatory response to immersion and falling skin and deep body temperature.

VENTILATORY RESPONSE TO IMMERSION: THERMONEUTRAL AND WARM WATER

The ventilatory responses to immersion in thermoneutral water are a direct result of the high density of water compared with air and the consequent differential hydrostatic pressure over the immersed body. A negative transthoracic pressure of ~14.7 mmHg is established on immersion that results in negative pressure breathing. A cephalad redistribution of blood occurs within six heart beats of immersion and can increase central blood volume by up to 700 ml. The increase in intrathoracic blood volume engorges the pulmonary capillaries and competes with air for space in the lung, resulting in a 30–50%

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reduction in static and dynamic lung compliance, whereas pulmonary gas flow resistance is increased by 30–58% and impedance by 90% (69). These shifts are thought to contribute to a small and transient increase in oxygen consumption during the first minute of immersion in water up to 40°C (51). The increase in pulmonary capillary blood volume seen on immersion in 34° and 40°C water, as a result of increased hydrostatic pressure, is not significantly increased on immersion in water at 25°C, suggesting that cold-induced vasoconstriction does not augment the blood volume shifts caused by hydrostatic pressure (11).

In conjunction with the increase in hydrostatic pressure on the chest, the hemodynamic alterations result in a 65% increase in the work of breathing. Vital capacity is reduced by an average of 6%, maximum voluntary ventilation by 15%, and expiratory reserve volume is decreased by an average of 66%, which results in a reduction in functional residual capacity (16, 17, 37).

The decrease in functional residual capacity and the increase in intrathoracic pooling of blood produces a small increase in pulmonary shunting; a small but consistent fall in the arterial partial pressure of oxygen has been reported by some authors (16) but not others (12). Opposing some of these impairments to lung function are improvements in both the ventilation-perfusion ratio and diffusion capacity of the lung.

From the practical viewpoint there is little evidence that the changes in lung function on immersion in thermoneutral or warm water threaten respiration in fit individuals.

VENTILATORY RESPONSE TO COLD IMMERSION: SKIN COOLING

Immersion of an unprotected body in cold water produces a large and fast fall in skin temperature, which, in turn, evokes the initial responses to cold immersion, given the generic name “cold shock.” This is probably the most dangerous response associated with immersion in cold water, having the potential to be a precursor to drowning or cardiovascular problems. It includes an “inspiratory gasp,” hyperventilation, hypocapnia, tachycardia, peripheral vasoconstriction, and hypertension (see Fig. 1; Refs. 40, 42, 70). The responses reach a peak within 30 s of immersion and adapt over the first 3 min of immersion in most individuals. The inspiratory gasp occurs almost immediately upon immersion, is usually between 2–3 liters in volume, and results in a corresponding inspiratory shift in end-expiratory lung volume (71). This results in breathing (hyperventilation) taking place within 1 liter of total lung capacity (26, 70). This shift, plus the large afferent drive to breathe, is probably responsible for the sensation of dyspnea experienced at this time, rather than bronchoconstriction or altered lung mechanics (43). The time course of the inspiratory shift corresponds with the period when subjects report being breathless (41).

The method by which individuals enter cold water has a significant effect on the pattern of respiratory responses, as the cold shock response shows both spatial and temporal summation. During the first 10 s of a staged immersion, frequency can

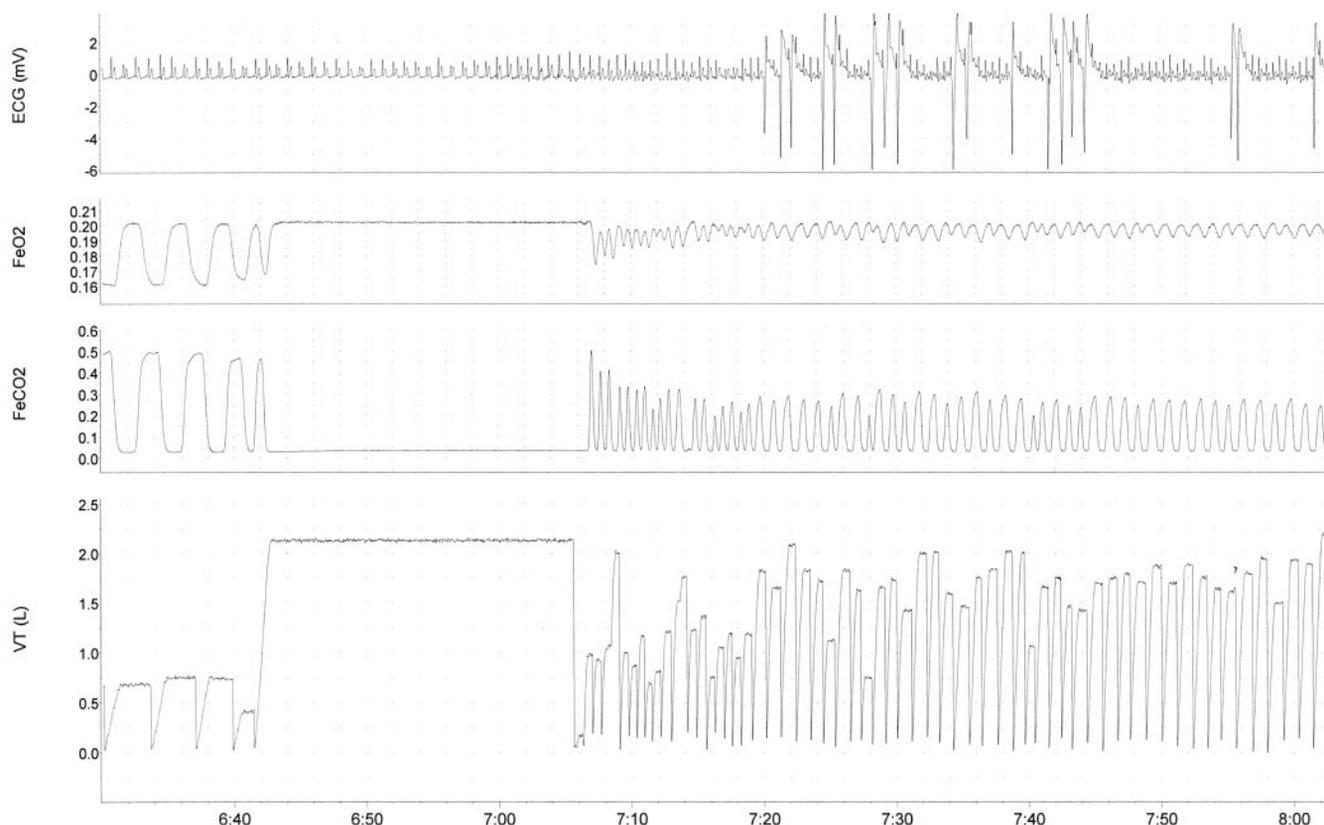


Fig. 1. Cold shock response in a normal male subject following breath holding during naked, head-out immersion in cold water (11°C). From *top* downward are shown the ECG (lead II), exhaled PO_2 (FE_{O_2}), exhaled PCO_2 (FE_{CO_2}), and tidal volume (VT). Despite the subjects' best efforts to voluntarily maintain apnea, breath-hold time is only 23 s. Note the cardiac arrhythmias, hyperventilation, tachypnea, and hypocapnia following the resumption of breathing.

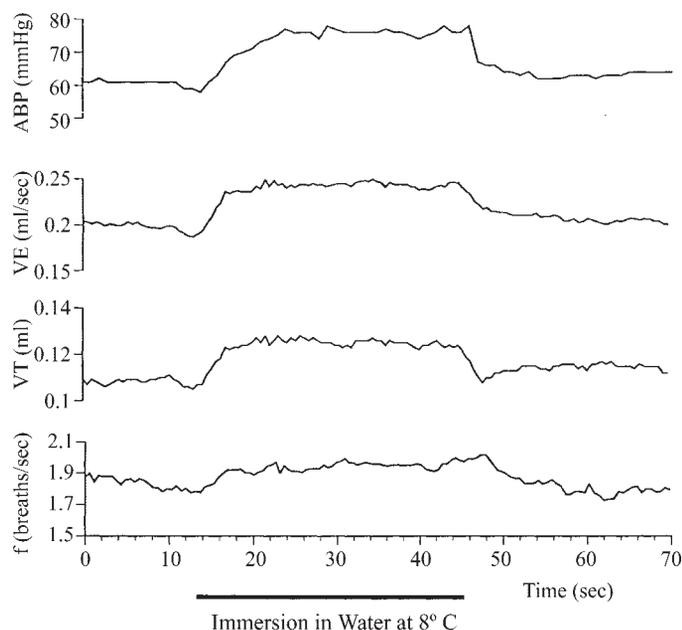


Fig. 2. Cold shock response in a tracheostomized rat, anesthetized with urethane. From top downward are shown arterial blood pressure (ABP), ventilation (\dot{V}_E), VT, and respiratory frequency (f). The horizontal bar indicates upright immersion to the diaphragm in cold (8°C) water, after which the rat is transferred back into 37°C water (Tipton and Harris, unpublished observations).

increase by 41% and ventilation by 278%; however, with a nonstaged immersion the increases are much greater: frequency 115% and ventilation 644% (31).

The cold shock response can reduce maximum breath-hold time to 25–30% of that seen before immersion, and breath holding is followed by hyperventilation and resultant profound hypocapnia (see Fig. 1 and Ref. 70). This hyperventilation occurs notwithstanding the increase in airway resistance to both inspiration and expiration on immersion noted above, implying that the drive to breathe is vastly increased. The fact that the ventilatory response is as large when immersion in cold water follows voluntary hyperventilation to lower carbon dioxide tension (71) is further evidence that the drive to breathe on cold immersion is great and is not attenuated by the chemoreceptor pathways that normally influence ventilation. Cooper et al. (15) reported that hyperventilation on cold water immersion occurs without an alteration in the sensitivity of the central chemoreceptors.

The initial respiratory responses to immersion in cold water occur before there has been any change in core temperature and the speed of the response indicates that they are neurogenic in origin. That the responses are not seen on immersion in warm water suggests that they are initiated by the cutaneous cold receptors, the superficial subepidermal location of which (depth ~ 0.18 – 0.22 mm) explains the speed of the response and that fact that it is not influenced by subcutaneous fat thickness.

The precise afferent pathways responsible for the respiratory responses to cold water immersion remain to be elucidated. It has been suggested that thermoafferents from the peripheral cold receptors directly stimulate the respiratory center (26). Keatinge and Nadel (43) concluded that the reflex respiratory responses to cold water in the cat are mediated at midbrain

level and that the cerebrum is not essential for the response. The earlier work of Lumsden (47) and St. John (66) sheds light on the neural pathways responsible for gasping. In vagotomized animals, eupnea is transformed to gasping following removal of the pons or during hypoxia (48). Furthermore, destruction of neurons in the rostral medulla with neurotoxins leads to the elimination of gasping but not eupnea (65), indicating that the neural pathways for gasping (an area in adult cats extending from dorsomedial and ventrolateral medulla, termed the pre-Bötzinger complex, to the nucleus ambiguus) may be distinct from those necessary for the generation of eupnea. That the first respiratory response to immersion in cold water is a gasp indicates that the cold thermoreceptor volley elicited by cold immersion excites this area.

Using *c-fos* protein immunohistochemistry (9, 33), Tipton M and Harris M (unpublished observations) have identified the neuronal cell groups activated following the cold shock response evoked (Figs. 2 and 3) by 60-s upright immersion to the diaphragm of rats in 8°C water. The *c-fos*-positive neurons were identified in the nucleus tractus solitarius, area postrema, and dorsal motor nucleus, that is, areas known to process cardiovascular and respiratory afferents. No expression was

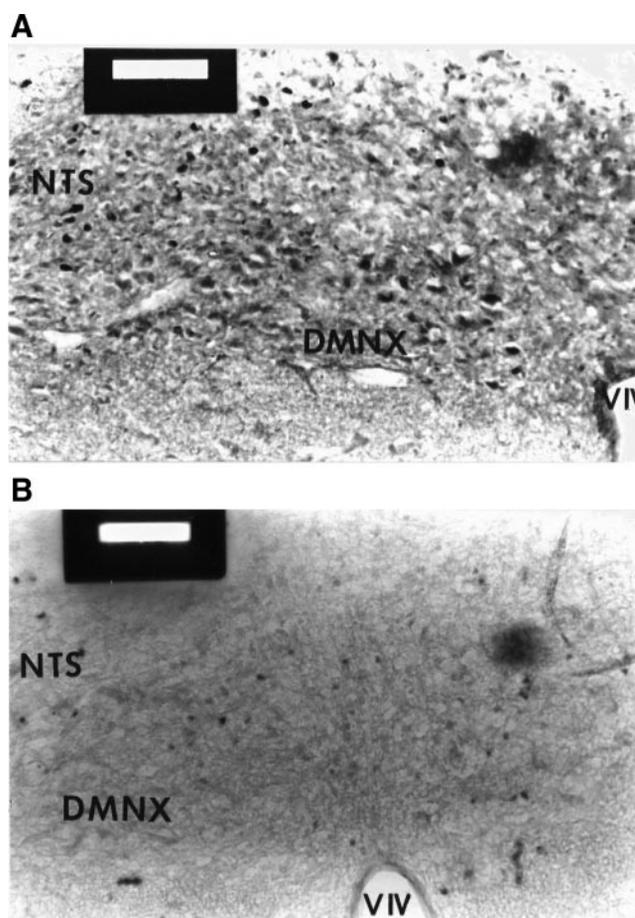


Fig. 3. *c-fos* proto-oncogene staining in the dorsal medullary nuclei of a urethane-anesthetized rat after immersion in cold water (8°C , 60 s, top) and thermoneutral water (37°C , 2 h, bottom). There is marked staining only during cold immersion in areas known to be responsible for cardiorespiratory integration. NTS, nucleus tractus solitarius; DMNX, dorsal motor nucleus of tenth cranial nerve (vagus); VIV, fourth ventricle. (M. Tipton and M. Harris, unpublished observations)

observed in animals immersed in water at 39°C (Fig. 3). Analogous studies from other groups show the pathway for noxious cold stimuli (hindlimb immersion in 4°C water) causes *c-fos* activation of neurons in lamina I of the spinal dorsal horn (1, 77). Another group showed that this *c-fos* immunoreactivity coreacts with NK-1 receptor staining, indicating that those receptors may mediate some of the noxious cold response (19). Other studies show that facial immersion in 4°C water causes *c-fos* activation of neurons in the dorsal horn of the medulla (67). These neuroanatomic studies corroborate the hypothesis that ascending neurons involved in transmitting the thermoreceptor volley following cold immersion are in the pons (4, 32) very close to the neurons involved in the generation of gasping.

ANTICIPATION, ANXIETY, AND STRESS COMPONENTS OF COLD SHOCK: POTENTIAL THERAPIES

The hyperventilation seen after the initial gasp of the cold shock response probably also reflects a stress response, which would be accompanied by a sympathetic overdrive (30). The speed of this response, as with the respiratory response, again suggests an uncomplicated neural pathway, thought to be mediated through the tegmentum of the midbrain and the hypothalamus (80).

The observation that many subjects display a tachycardia and relative hyperventilation before they are immersed in the cold water provides further evidence that an anticipatory anxiety and stress response is occurring (68) to the cold immersion. Animal studies suggest that acclimation to this stress response may involve endogenous opioid production (36).

Confirmation that there are neurogenic changes accompanying the cold shock response comes from human studies measuring cerebral blood flow velocity (76). Those authors demonstrated that middle cerebral artery blood flow was reduced during cold (12°C) water immersion compared with that recorded in water at 35°C (see Fig. 4B). However, if the hyperventilation-induced hypocapnia induced by cold shock was matched by voluntary hyperventilation either in warm air (24°C; see Fig. 4A) or thermoneutral water (35°C), there was an even lower cerebral blood flow velocity. In other words, the cerebral blood flow velocities seen during cold shock are higher than one would expect for a given level of arterial carbon dioxide, suggestive of either increased cerebral neurogenic activity with an accompanying demand for increased cerebral blood flow, or systemic sympathetic-induced hypertension.

Recent evidence from our laboratory suggests that there is also a marked and modifiable psychological component to the breath-hold component of the cold shock response (6). Subjects were asked to breath hold in air and then during immersion into stirred cold water. As expected, the breath-hold times were markedly reduced from 46 s to only 24 s despite subjects' best efforts to maintain apnea volitionally. This was accompanied by tachycardia and, after the break of breath hold in water, a profound hyperventilation and hypocapnia (nadir PCO_2 22 Torr), indicative of a powerful sympathetic overdrive. The subjects were then split into two groups, matched for breath-hold time. One group was given a battery of psychological skills: goal setting (46), arousal regulation (58), mental imagery (44), and positive self-talk (29) over 5 days. The mean breath-hold time of this group increased to 44 s during a second

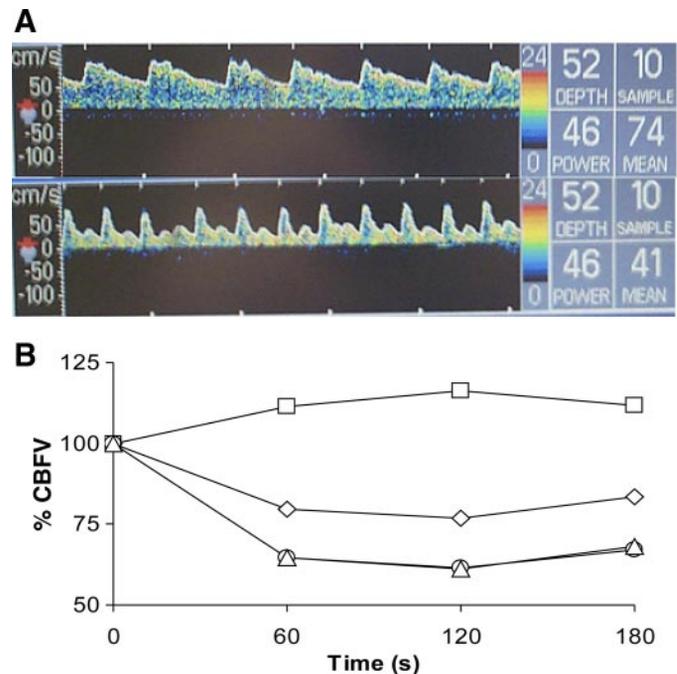


Fig. 4. A: cerebral blood flow velocity (CBFV) of human middle cerebral artery recorded with Doppler ultrasound in a normal adult male subject. *Top*: CBFV recorded over 5 s at rest. *Bottom*: CBFV during hyperventilation with end-tidal PCO_2 (PET_{CO_2}) matched to that seen in the same subject during cold water immersion. B: group results of CBFV of human middle cerebral artery over 3 min in 8 healthy adult volunteers. Data for immersion in thermoneutral water (35°C, □), cold water (12°C, ◇), room air (24°C, △) with PET_{CO_2} matched to cold water immersion, and immersion in thermoneutral water (35°C, ○) with PET_{CO_2} matched to cold water immersion are shown prior to intervention and at 1, 2, and 3 min after the intervention. Note that cold water immersion (◇) results in a decrease in CBFV secondary to hyperventilation and consequent hypocapnia. However, this level of CBFV is greater than that seen in thermoneutral water and room air once the level of CO_2 is matched (76).

immersion 1 wk later, whereas that of the control group who had not received the psychological skills training remained at 21 s. A corresponding change was not seen with the heart rate response before or during immersion.

Thus the psychological skills had influenced the respiratory but not the cardiac component of the cold shock response, the obvious difference between the two being the degree to which they are under conscious control. Breath holding requires the voluntary suppression of a drive to breathe; in cold water this drive comes from the cutaneous cold receptors. It is most likely that the psychological skills improved the ability of subjects to volitionally suppress the cold-evoked drive to breathe and maintain voluntary apnea for longer. This implies an enhancement of the descending inhibitory cortical pathways to the respiratory centers.

The initial respiratory responses to immersion in cold water can habituate. As few as five 3-min immersions in cold water can reduce these responses by 50% (74), with the response still being reduced by 25% 14 mo later (75). The extent to which habituation of the initial respiratory responses to immersion is a psychological phenomenon remains to be determined. That the alterations that underpin habituation occur central to the peripheral cold receptors has been established; repeatedly immersing one side of the body habituates the respiratory response evoked by a single immersion of the other, previously

unexposed, side of the body (73). Little has been done to identify the neural pathways associated with the habituation of the initial respiratory response to cold water immersion. More is known about the habituation of the heart rate response to repeated cold exposure. Glaser and Griffin (25) reported that small bilateral frontal lesions of the cerebral cortex in rats prevented the habituation seen in heart rate following repeated cold water immersion of their tails. However, such lesions only abolished established habituation in 25% of the rats tested. They concluded that the frontal areas of the cerebral cortex were necessary for the achievement but not the maintenance of habituation. After experiments in which the blood pressure and heart rate responses of leukotomized and control subjects were examined during repeated immersion of the hand in 4°C water, Griffin (28) concluded that the frontal areas of the cortex are also important for the establishment of habituation in man. The habituation of blood pressure, heart rate, and subjective responses induced by repeated hand immersion in 4°C water can be abolished by 75 mg of chlorpromazine taken orally. However, the wide-ranging postsynaptic antagonistic effects of this drug do not help elucidate the precise pathways responsible for habituation.

CARDIAC ARRHYTHMIAS ON COLD IMMERSION: AN INTERACTION BETWEEN RESPIRATORY AND CARDIAC REFLEXES?

Ectopic cardiac beats have been noted during the initial stages of head-out cold water immersions even in healthy normal or elite divers (62) and even in water as warm as 25°C (20). Cardiac arrest is a rare but documented cause of death when water enters the nostrils (39), indicating that the cardiac component of the cold shock response may be a precursor to sudden death on immersion and requires further investigation. Wet- and dry-suited subjects submerged under cold-water experience supraventricular arrhythmias during and after breath holding (62, 72). The interpretation of the results of these studies is complicated by subjects being submerged and hence subject to trigeminal nerve stimulation of the face, eliciting the diving response of bradycardia, apnea, and hypotension (34). Secondly, the subjects wore protective clothing, so the cold stimulus to the subjects' skin was attenuated. Thirdly, the study could not address the question as to whether the cardiac arrhythmias observed were in some way related to the act of breath hold and its release. Lastly, the study could also not exclude the possibility that the arrhythmias seen were the result of a hydrostatic squeeze on the body from immersion per se resulting in an increase in venous return to the heart and consequent cardiopulmonary reflex activation. To overcome these confounding variables, we recently investigated two groups of subjects wearing just swimming trunks undertaking head-out immersion in stirred cold water 1) during and after breath holding and 2) during free breathing (18). Under these circumstances, subjects were not submerged and therefore there was no complication from the diving reflex, and the absence of protective clothing meant that all subjects were exposed to an unattenuated cutaneous cold stimulus. Furthermore, both groups of subjects experienced the same hydrostatic squeeze but only in the first group did breath holding occur.

A tachycardia was seen before immersion in both groups, which was ascribed to an anxiety- and anticipatory-related

sympathetic overdrive; both groups were also subject to a tachycardia during immersion ascribed to a continuation of that sympathetic overdrive. However, cardiac arrhythmias (predominantly supraventricular and junctional) were seen in over 60% of the first group after release of breath holding but not in the free breathing group. This compares with an incidence of 81% of the submersions of Tipton et al. (72); the greater prevalence with submersion is probably due to the greater vagal drive seen with face immersion and trigeminal nerve stimulation.

We conclude that the cardiac arrhythmias are the result of the interaction of release of breath holding in a cold milieu and not ascribable to a hydrostatic effect on the subject. This is confirmed by previous work from our laboratory on horizontal immersion in cold water, where hydrostatic effects on the subject were minimal, yet ECG arrhythmias are also seen at the break of voluntary breath holding (M. Tipton, unpublished observations). It is also notable that the arrhythmias were often time linked to respiration; this was also observed by Tipton et al. (72) and interpreted as suggesting that the arrhythmias were in part due to a cyclical vagal stimulus to the heart. We therefore propose that immersion into cold water results in three distinct patterns of response: 1) face-only stimulation by water, even when cold, leading to a diving-reflex mediated bradycardia; 2) anticipation, anxiety, and cold cutaneous stimulation leading to a sympathetic overdrive and tachycardia; and 3) release of breath holding in cold water, producing supraventricular and junctional arrhythmias in 60% of head-out immersions and ~80% of submersions when the vagal tone is raised still further. An integrated model of the cardiorespiratory response to cold shock incorporating these elements has been developed (21).

POSSIBLE APPLICATIONS AND ASSOCIATIONS: SURVIVAL, BIRTH, SLEEP, AND SUDDEN DEATH

The marked reduction in breath-hold time (i.e., volitional apnea) with cold water immersion and submersion has obvious implication for escape from within vessels, helicopters, and vehicles that have accidentally sunk, as well as immersion in rough water. The volume of the inspiratory gasp and the minute volumes resulting from the uncontrollable hyperventilation (minute ventilation >100 liters) that occurs on immersion in cold water should be compared with the lethal volume for sea water aspiration, 22 ml/kg or ~1.5 liters for a 70-kg human (52). The observation of the high incidence of cardiac arrhythmias following the release of breath hold has implications for snorkeling and breath-hold diving, as well as for survival following near drowning.

In many countries, water birth has become commonplace. For example in the United Kingdom, the UK Central Council for Nursing has stated that assistance at water birth is part of a midwife's duties and not "special treatment" (13, 78). Each midwife needs to be confident that she has skills to help women give birth in water. For some time it has been thought that the vagally mediated triad of responses to trigeminal nerve stimulation (apnea, bradycardia, and selective vasoconstriction) that constitute the oxygen conserving "diving response" (7, 34) provides protection against drowning for babies during underwater birth by conserving oxygen (61). However, it is known that the response in neonatal animals is markedly diminished in

the presence of hypoxemia, as can occur with a difficult delivery (27), and recently underwater birth has been linked to neonatal distress and mortality as part of a near-drowning scenario with radiological evidence consistent with lung aspiration of birthing pool water (38, 24). Thus it appears that the apnea associated with the diving response is insufficient in newborn babies to ensure that water is not inhaled during underwater delivery.

The presumed increased sympathetic drive with tachycardia and subsequent arrhythmias seen after the break of the volitional apnea during cold immersion is analogous to the cardiac changes observed in obstructive sleep apnea. Obstructive sleep apnea is a common condition in adults and has been associated with arrhythmias. There is a peak in sudden death of cardiac cause between midnight and 6 AM. The severity of sleep apnea is proportional to the risk of sudden cardiac death (22). Furthermore, atrial fibrillation, ventricular ectopics, and second-degree heart block and even complete heart block requiring intervention of a pacemaker have been seen (45). Many of these arrhythmias occur after the period of apnea, reminiscent of the cardiac arrhythmias seen after breath holding during cold immersion. Use of microneurography in patients with sleep apnea confirms that there is a significant sympathetic overactivity in sleep apnea (53), which may be responsible for both the hypertension and the cardiac arrhythmias seen in patients with sleep apnea to a far greater degree than in weight-matched obese control patients (54). That the sympathetic hyperactivity normalizes with elimination of apnea and regularization of breathing after continuous positive airway pressure therapy lends credence to this hypothesis (54). There is thus emerging a credible chain of evidence linking apnea and its release, a sympathetic overdrive and the generation of potentially life-threatening arrhythmias with an increased risk of sudden death.

Finally, on the topic of the potentially harmful interaction of respiratory and cardiac responses, it is worth noting the link between immersion, the cardiac disorder of long QT syndrome (LQTS), and sudden death. Over 4,000 people between the age of 1–22 yr suffer sudden unexplained death each year in the United States. LQTS is a genetic disorder for which multiple genes have been identified, all of which encode cardiac ion channels. In LQTS there is abnormal ventricular repolarization and increased risk of malignant ventricular tachyarrhythmias (e.g., Torsades de pointes). Swimming appears to be a gene-specific arrhythmogenic trigger for the LQT1 genotype of LQTS (2). Ishikawa et al. (35) reported that 51 of 64 children with known arrhythmias developed significant arrhythmias while swimming or diving. LQTS cannot be identified post-mortem without molecular diagnoses. This leads to the possibility that some unexplained immersion deaths could have a genetic basis.

It remains to be determined how swimming triggers the degeneration of a stable rhythm, but swimming combines exertion, voluntary apnea with accompanying oxygen desaturation, possible cold exposure, and face immersion. As noted above, the combination of the cessation of breath holding and vagal stimulation can represent a potent arrhythmogenic stimulus in some situations, notably when the sympathetic nervous system is coincidentally stimulated. This combination of stimuli may also have a role in the arrhythmias seen in LQTS. Yoshinaga et al. (81) have reported that, in children with a high probability of sporadic LQTS, cold water face immersion

results in much longer QT intervals than those seen in control children.

VENTILATORY RESPONSE TO COLD IMMERSION: DEEP BODY COOLING

In the absence of shivering, which increases metabolic rate and ventilation, patients with accidental hypothermia frequently demonstrate respiratory depression that leads to carbon dioxide retention and acidosis (49). Most slowing of breathing occurs with cooling from normothermia to deep body temperature of 32–34°C. This suggests that some aspect of respiratory control is abnormal during hypothermia. This abnormality does not appear to be associated with the mechanical properties of the respiratory system, which do not change significantly in hypothermia down to a temperature of 29°C (63). Respiratory rate, tidal volume, and minute volume all fall during hypothermia (3, 10) in proportion to the reduction in metabolism (57). Vital capacity is also reduced, probably, as already noted, because of filling of the pulmonary capacitance vessels.

Slowing of breathing is seen at deep body temperatures above the threshold for blunting of the ventilatory response to hypercapnia (55) and results in carbon dioxide retention and acidosis. This suggests that the metabolically linked slowing in breathing frequency during mild hypothermia is due to alterations in the brain stem neuronal systems for the generation of eupneic breathing per se rather than any alteration in the response to the chemoreceptive drive.

Rewarming studies in anesthetized cats who were made hypothermic (23) have explored further the differences in temperature thresholds for effects on breathing frequency and volume; as core temperature rose, the increase in ventilation occurs via an increase in respiratory volume until core temperature exceeded 30°C, when increases in ventilation are due purely to increases in respiratory frequency.

Whole body cooling produces central vagal inhibition; this results in a bronchodilation that overrides the bronchoconstriction effect of airway cooling (64). In hypothermic humans, the transfer of carbon dioxide from the pulmonary capillaries is normal, and the single most important potential cause of hypercapnia is the reduction in the rate of alveolar ventilation. That alveolar P_{CO_2} can be low during hypothermia is due to the fact that carbon dioxide production can be suppressed more than alveolar ventilation (the carbon dioxide production of the body is approximately halved by an 8°C fall in deep body temperature). However, below a deep body temperature of ~32°C, decreased spontaneous respiratory activity, plus increased solubility of carbon dioxide in the body fluids, can result in respiratory acidosis and severe hypercapnia (14). The respiratory failure of hypothermia can also result in hypoxia, sometime profound, with arterial P_{O_2} as low as 3.3 kPa (25 Torr) (56). The hypoxia can be compounded by the increased oxygen demand associated with shivering. Although the provision of pure oxygen can assist in correcting the hypoxia, it also removes the hypoxemic stimulus to breathe; this may be the primary drive to breathe in those with severe hypothermia and its removal can result in respiratory arrest (50).

In conclusion, cold water immersion represents a potent stimulus to the respiratory system, one that can override both conscious and other autonomic respiratory controls to act as a precursor to drowning. The combination of the reestablishment

of respiratory rhythm after breath holding, hypoxemia, and coincident sympathetic nervous and vagal stimulation appears to be the arrhythmogenic trigger for potentially hazardous response in a range of conditions, including those seen during submersion, birth, sleep, and sudden death. Immersion in cold water is the most common scenario in which these factors coexist. It is concluded that the respiratory responses seen on immersion can represent a significant threat to life.

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