A recent report of the World Health Organization (WHO) labels drowning as one of the world's leading causes of death (164). Although standard WHO statistics report almost 375,000 persons drowning each year, the actual figure for world-wide drowning is probably four or five times as high. Low- and middle-income countries, where most drownings occur, have incomplete recording of drowning events. Furthermore, drowning as a result of flooding, ferryboat accidents, and accidents with boat-carrying refugees and migrants are not reported in the standard drowning statistics (140, 164).

Drowning is formally defined as the process of experiencing respiratory impairment from submersion/immersion in liquid (273). The exact physiological mechanisms of this process are complex and largely unknown, and have only been speculatively described in drowning reviews and studies over recent decades (29, 108, 132, 195, 257). Although there are clinical differences between submersion and immersion (30, 275), the details of the physiological processes have not been reviewed. The present work provides an overview of the current understanding of the physiological mechanisms that may occur during a submersion or immersion incident. Since human drowning mechanisms per se are difficult to study, observations from animal experiments, case series, and forensics have been included where helpful.

The objective of the review is to summarize the physiological mechanisms associated with drowning and to explore whether future physiological studies may contribute to the prevention, treatment, and forensic investigations of drowning.

A final problem with hypothermia is that, in the field and sometimes in the emergency department, the absence of a reliable measure of deep body temperature makes the direct and accurate assessment of the degree of hypothermia in an immersion victim difficult (150 , 258).

The variation in the rates at which people cool in water below thermoneutral temperatures, and the poor association between the signs and symptoms of hypothermia and actual deep body temperature, make the determination of time of useful consciousness and survival time â€œmore of an art than a scienceâ€• (88). It also follows that the signs of hypothermia may be unreliable indicators of deep body temperature. For example, the presence and absence of shivering have variously served as indicators that body temperature is normal, under threat, or profoundly hypothermic. However, shivering is dependent on functioning neuromuscular pathways, blood glucose levels, and a local supply of substrate (82); these factors may change, independent of deep body temperature. Hypoglycemia following consumption of alcohol, a common factor in immersion victims, can suppress shivering independent of body temperature (94). Substrate depletion is more likely in chronic hypothermia than in the acute hypothermia observed in immersion victims.

As noted, during accidental hypothermia, the deep body temperature associated with death is â‹¼25Â°C (5), but the lowest deep body temperature recorded to date following accidental exposure to cold air and with a beating heart and full

recovery was 12.7Â°C in a 28-mo-old child (19 , 217). The coldest adult survivor of cold-water immersion followed by submersion had a body temperature of 13.7Â°C (86).

The signs and symptoms of progressive hypothermia are not strongly correlated with temperature. The temperatures above in parentheses are only rough approximations. Great variation exists between individuals in both the rate of cooling and the lowest deep body temperature compatible with life or consciousness (5). The rate of cooling depends on a wide range of internal thermal factors including subcutaneous fat thickness (119 , 213) or nonthermal factors like motion illness (167) and external factors such as water temperature and sea state (88). Table 2 provides an overview of the risk factors for development of immersion hypothermia.

A distinction should be made between induced hypothermia for clinical purposes and accidental hypothermia. Successful resuscitation has occurred following induced hypothermia down to deep body temperatures as low as 5Â°C (32). In contrast, in accidental hypothermia, it is not uncommon for death to occur at a body temperature of 24â€“28Â°C. Therefore, the circumstances of cooling and rewarming resuscitation, and associated changes in physiology in themselves, can be important determinants of survival. In addition, different physiological functions have different susceptibilities to cooling. The Q 10 temperature coefficient is a measure of the rate of change of a biological or chemical system as a consequence of increasing/decreasing temperature by 10Â°C. For example, metabolic and rhythmic processes are particularly depressed by hypothermia (Q 10 of âˆ¼3); contractile processes have a Q 10 of âˆ¼2. As hypothermia progresses, metabolic and rhythmic processes are depressed two to three times more than the rates of diffusion of different metabolites (152). Some of the mechanisms underpinning the functional changes associated with hypothermia are briefly outlined in (see Table 1). Although presented separately, it should be apparent that these changes are interrelated.

The progressive signs and symptoms are shivering (36Â°C), confusion, disorientation, introversion (35Â°C), amnesia (34Â°C), cardiac arrhythmias (33Â°C), clouding of consciousness (33-30Â°C), LOC (30Â°C), ventricular fibrillation (VF) (28Â°C), and death (25Â°C). Below a cardiac temperature of 28Â°C, the heart may suddenly and spontaneously arrest. VF may result from rough handling of the casualty at deep body temperature of âˆ¼28Â°C (88 , 89). Hypothermia affects cellular metabolism, blood flow, and neural function. In severe hypothermia, the patient will be deeply unconscious. The decreased oxygen requirement of cold cells and organs causes decreased respiratory and heart rates. This makes it difficult to detect vital signs in the field. Tendon reflexes are absent and the pupils dilated: this may give the

appearance of death (88).

With regard to drowning, the most significant consequence of hypothermia is the loss of consciousness (LOC) with deep body cooling. This prevents individuals from undertaking physical activity to maintain a clear airway.

The detrimental influence of peripheral and deep-tissue cooling on physical performance has recently been reviewed (43). It is noteworthy that drowning caused by physical incapacitation can occur before deep body tissue temperature falls below 35Â°C.

At nerve temperatures below âˆ¼20Â°C, nerve conduction is slowed and action potential amplitude is decreased (62). Ulnar nerve conduction velocity falls by 15 m/s per 10Â°C decrease of local temperature. Nerve block may occur at a local temperature of between 5 and 15Â°C for 1â€“15 min and lead to a dysfunction that is equivalent to peripheral paralysis (22 , 50).

After the skin has been exposed to cold water, the next tissues to cool are superficial nerves and muscles. Those in the arms are particularly susceptible due to the surface area-to-mass ratio of the arms and the relatively superficial anatomical location of nerves and muscles. Low muscle temperature can affect chemical and physical processes at the cellular level. This includes metabolic rate, enzymatic activity, calcium and acetylcholine release and diffusion rate, and series elastic components of connective tissues (278). At muscle temperatures below 25Â°C, fatigue occurs because cooling impairs superficial muscle fibers leaving a smaller number of fibers to produce the same force (50). Maximum dynamic strength, power output, jumping, and sprinting performance have been related to muscle temperature with reductions ranging from 4 to 6% per degree fall in muscle temperature down to 30Â°C (27 , 213).

At the same time, upon initial immersion in cold water, the incidence of arrhythmias increases from 2% during cold water immersion with head-out-of-water free-breathing to 82% if the cold immersion is associated with face immersion and maximum breath-holding (see section Diving Response and Autonomic Conflict below).

The â€œbreaking point curveâ€• defines the values of alveolar Po 2 and Pco 2 at the breath-hold break point when starting from different states. The normal alveolar starting point is shown. This point is displaced by different maneuvers, and the length of the arrows gives an indication of the changes of the breath-hold duration. See Refs. 73 , 196. a, After breathing 15% oxygen; b, after hyperventilation; c, normal alveolar point; d, after breathing 30%

oxygen.

Cold receptors respond to the sudden decrease in skin temperature resulting from immersion in cold water with a dynamic response that evokes gasping, hyperventilation, increased cardiac output, peripheral vasoconstriction, and hypertension. These responses, along with a generalized increase in muscle tension, can increase metabolic rate on initial immersion by a factor of four (98). This would, on its own, decrease breath-hold time during initial immersion because the hypoxic and hypercapnic thresholds for the breakpoint of breath-holding would be reached earlier (FIGURE 1). More important, thermo-afferents from the peripheral cold receptors dramatically increase respiratory drive via direct stimulation of the respiratory center (121), with a reflex stimulation at the spinal level of Î±-motoneurons innervating the intercostal muscles and diaphragm (166 , 263). As a consequence, the gasp response and hyperventilation cause an inability to breath-hold. Maximum breath-hold time generally is 60â€“90 s at a comfortable air temperature and is reduced to just a few seconds in water colder than âˆ¼15Â°C. The inability to breath-hold represents the most hazardous response to cold-water immersion, increasing the chance of aspiration and drowning.

After a fall into cold water, any intention to breath-hold can be overcome by cold shock (261 , 263). The response starts in water âˆ¼25Â°C and peaks somewhere between 15 and 10Â°C; it peaks in the first 30 s of immersion and attenuates during the next 2â€“3 min (268). It is evoked by cold receptors located in the superficial sub-epidermal layer of the skin; below âˆ¼19Â°C, cold nociceptors contribute to the response with a sensation of intense cold pain being experienced in water below âˆ¼5Â°C (40 , 163). The cold-shock response may be decreased but is still present in those with a high body temperature (159).

Most drownings occur in water colder than thermoneutral temperature, thus initiating physiological responses associated with cooling. In cold water, the responses that act as precursors to drowning are evoked by skin cooling (cold shock), then cooling of superficial nerves and muscles in the limbs, and finally cooling of deep body tissues (hypothermia).

Competitive swimming in warm water can cause a marked increase in deep body temperature and insidious hyperthermia. The pathophysiology of endurance swimming in warm water has been considered after a death during warm-water competition (260). Hyperthermia during diving in tropical waters also can pose a drowning risk (208 , 260).

Increased HR may trigger ventricular arrhythmias, potentially hazardous in combination with peripheral vasodilatation and increased blood viscosity (229). The associated dehydration increases likelihood of thrombosis, particularly in the elderly (158 , 239). HWI drowning is most likely to occur during protracted immersion at high temperature and when leaving the tub (1 , 117). The loss of the hydrostatic squeeze on leaving a bath and assuming an upright posture can cause a gradual or sudden decrease in blood pressure (44 , 109 , 118 , 185 , 211 , 229 , 291). The HWI-related cardiovascular changes may be important in the elderly and in those with coronary artery disease, hypertension, or congestive heart failure (7 , 25 , 48 , 81 , 117 , 175 , 211 , 291).

Thermoregulation during HWI differs from thermoregulation in hot ambient air. In ambient air, elimination of body heat occurs mainly by sweat evaporation. The phase-change from a liquid to a gaseous state removes heat from the skin and cools the body. In HWI, the high humidity of the ambient air around a hot tub, with only the head and neck skin above the water, allows limited evaporation of sweat above the water. Sweating, however, also occurs under water. The secretory pressure of sweat glands allows sweat to flow outward to dissolve in the water. This sweat fails to evaporate and thus does not contribute to body cooling. When skin temperature increases, cutaneous warm thermoreceptors located in sensory nerve (unmyelinated C-type fiber) endings interact with keratinocytes through transient receptor potential vanilloid cation channels and convey signals, via the spinal dorsal horn and trigeminal nerve, to hypothalamic thermoregulatory centers mainly situated in the pre-optic area (220 , 235 , 237). From the pre-optic area, autonomic efferent information is forwarded to the skin and causes, among other effects, cutaneous vasodilatation (118 , 169 , 182). Under normal circumstances, external hydrostatic pressure results in bradycardia. In HWI, however, the temperature effects overcome this (16 , 34 , 236 , 251), because decreased peripheral vascular resistance raises heart rate (34 , 48 , 175 , 259 , 284).

Ofuro bathing is a component of Japan's national culture and identity. It is believed that healthy persons may benefit from the physiological effects of hot-water immersion (HWI) on the body's homeostatic systems (16 , 25 , 48 , 53 , 81 , 118). People may sit and soak up to the shoulders or neck in deep hot (38-43Â°C) tubs for 5â€“15 min (96 , 118). The high incidence of Japanese hot-water tub fatalities suggests that HWI may lead to drowning (2 , 109 , 175 , 191 , 211 , 291).

â€œThermoneutralâ€• is the term for the water temperature at which heat loss equals heat production (53 , 238). Most drowning events occur at water temperatures below the point of thermoneutrality, which is 35Â°C Â± 0.5. Some drownings, however, occur in hot-water tubs, while pouring hot water over the head, or during diving or competitive

swimming in warm water.

Submersion

Sympathetic Activation, Fear of Drowning Fear of drowning as a mechanism that results in drowning is most often reported in the gray literature and social media. Several triathletes mention excessive panic, notably during the mass start of swimming. The panic is accompanied by complete inability to swim. The fear of drowning urges them to go back to shore or get attached to a buoy or lifeboat. Approximately 80% of triathlon deaths occur during the swim, and it is speculated that several drownings during triathlon swimming may be due to the results of these panic attacks (39, 260, 264). Also, competitive swimmers may panic when swimming in open water where they are confronted with a different setting than the Olympic pool and the need to use different swimming strokes than the strokes they are trained for (260, 264). Recreational swimmers in open water encounter similar panic experiences when suddenly confronted with cold water, rip currents, or unexpected underwater objects. Some swimming instructors have experienced students who refused to enter the water or almost drowned when in the water, paralyzed by this fear of drowning. Special training programs have been developed for these students and are also recommended for experienced swimmers (114, 181). Divers with self-contained underwater breathing apparatus (SCUBA) also may panic when experiencing the sensation of cold and streaming water, losing visual contact with the bottom (blue orb syndrome), observation of large or dangerous fish, entanglement, entrapment, or equipment malfunction. This is sometimes combined with a reduction of muscle force (see below). An unknown, but probably significant, contributor to SCUBA drowning may be panic that completely incapacitates the diver both mentally and physically (181, 210). The psychological aspects in these situations also includes concern by the person in the water about a sudden onset of previously diagnosed and treated minor physical problems (such as cardiac problems, hypertension, diabetes) and other frightening thoughts, leading to sensory deprivation, illusions, flashbacks, and thoughts of catastrophic outcome. It is well known that panic leads almost instantaneously to irrational logic and cognition. Problem-solving capacities are decreased. There is limited physiological literature on this phenomenon, although many reports also mention a physical component, most of all paralysis or loss of muscle strength. This may be due to the hyperarousal of the sympathetic activation during panic in the water. This will lead to a combination of physical and psychological stressors that could potentiate cold shock, disable swimming ability, or at least create the feeling that swimming ability has seriously decreased. Notable in people with an overreactive anxiety state, the stressful or unexpected event may result in a panic-induced hyperarousal, resulting in submersion.

Breath-Holding Breath-holding has served as an intervention to discover more about control of breathing and

determinants of breath-hold time. A long history of excellent work has examined breath-holding physiology (78, 104, 200). Under normal circumstances in air, an initial period occurs with little respiratory afferent activity and therefore also with little effort required to maintain a breath-hold (â€œeasy going phaseâ€•). This ends due to afferent neural input to the respiratory centers arising from the respiratory musculature, creating an increasing drive for respiratory movement: the struggle phase (FIGURE 2). Respiratory movement, in the form of rebreathing into a bag at the point of maximum breath-hold, can double the time spent without fresh air (78). The respiratory movement associated with re-breathing decreases the afferent neural input arising from the respiratory musculature and extends the breath-hold time to the point where blood oxygen and carbon dioxide tensions drive respiration. Swallowing can extend breath-hold time by causing some movement of the respiratory musculature, perhaps explaining why some drowning victims have water in their stomachs when rescued. Under normal circumstances, typical alveolar Pco 2 at the breakpoint ranges between 43 and 53 Torr and occurs 60â€“90 s after breath-holding with ambient air (FIGURE 2). The breath-holding time can be influenced by several factors, including those listed in Table 3 (196). FIGURE 2.Human thoracic movements measured by electromyography (EMG) during maximal breath-holding in an untrained, non-immersed subject â€œEasy going phaseâ€• and â€œstruggle phaseâ€• are distinguished by the absence or presence of respiratory muscle activity that must be suppressed during breath-holding. Figure is from Ref. 72 and used with permission from Saunders. Download figureDownload PowerPoint

Table 3 Factors influencing breath-holding duration in air Metabolic rate during breath-holding Prebreathing with hyperoxic or hypoxic gas mixtures Carbon dioxide and oxygen storage capacity Prior hyperventilation Experience and psychological tolerance of unpleasant sensations arising during breath-holding In water, important additional physiological factors decrease breath-holding duration, including alcohol intoxication, water temperature below â‹¼15Â°C, and the cold shock response that intensifies respiratory drive. Other factors that can influence breath-hold time include voluntary liquid aspiration such as occurs in suicides. As with many physiological responses that involve a combination of autonomic and conscious input, the variation between individuals in maximum breath-hold time is large. Even in the same cold water temperature, the breath-hold time can range from 100 s (262). In warm water, the average maximum breath-hold time is â‹¼45 s, but some trained breath-hold divers can achieve over 20 min (149, 252a).

Diving Response Whereas there is evidence that the diving response conserves oxygen during apneic diving or cold exposure of the face, only limited and indirect evidence defines the role of the diving response during drowning. The diving response is one of the commonly proposed mechanisms to explain why some drowning victims survive for prolonged periods underwater (91). However, the response is probably much less important as a protective mechanism than is rapid

selective brain cooling caused by the supply of cold carotid blood to the brain and cooling of the heart caused by the aspiration and ingestion of ice-cold water (51, 90, 266, 270). Research into diving birds, reptiles, mammals living in or underwater, and other hypoxia-tolerant animals shows that the diving response is an autonomic response that serves as an endogenous hypoxia defense mechanism to preserve life. The diving response is better developed and has a faster onset in diving mammals and children than in adult humans (47, 77, 91, 106, 137). Rats have been trained to dive to allow study of the diving response (106, 161, 162, 198). Studies with infants reveal that, up to 6 mo of age, all children have the ability to achieve the diving response. This is decreased to 90% of all children at 12 mo of age (87, 207). The diving response could be triggered in 66% of adult volunteers, but with large interindividual differences in its effects (99). Human studies are mostly related to breath-hold diving (9, 95, 97, 102, 133, 134, 137) and facial immersion in cold water (38, 126). The diving response is considered one of the most powerful autonomic responses, particularly in children (42, 198). For this reason, clinically relevant studies on the diving response have involved treatment of paroxysmal atrial tachycardia, diabetic cardiovascular autonomic neuropathy, and rheumatoid arthritis (42). Because the diving response is an oxygen-conserving response, it is also used as a potential model to study endogenic neuronal protection effects at the molecular level (105, 227). It is also used to teach integrative physiology to students (45). The diving response can be activated by apnea alone or by facial immersion alone, but their combination enhances the response (4, 11, 42, 45, 97). Most important is the presence of cold water and a large ambient air-to-water temperature gradient (77, 233). The diving response involves simultaneous activation of sympathetic and parasympathetic responses leading to peripheral vasoconstriction, hypertension, and bradycardia (FIGURE 3) (42, 203). Individual papers debate whether apnea, laryngospasm, or contractions of the spleen are part of the response (87, 232). The effects have been consistently observed in studies, with large individual differences. The diving response decreases metabolism selectively, mainly in the vasoconstricted tissues and heart, resulting in an overall decrease in oxygen consumption and a slower desaturation during apnea. This is in contrast to protective hypothermia that decreases the metabolism and oxygen consumption of all organs. The factors that influence the effects of the diving response are summarized in Table 4. FIGURE 3.Schematic figure of the diving response Input appears on the left and output at the right. In between are the neural connections located in the nucleus tractus solitarius and central nervous system control centers. The response is activated through the chemoreceptor sensitivity of the cold receptors of the skin and the unmyelinated C-fibers of the ophthalmic branch of the nervus trigeminus. For more details on the neurological pathways of the diving response, see also Refs. 162, 199, 226, 234. +, Excitatory neural connections, âˆ’, inhibitory neural connections. Figure is from Ref. 77 and used with permission from Scandinavian Journal of Medicine and Science in Sports. Download figureDownload PowerPoint

Table 4 Factors that increase effects of the diving response (10, 11, 17, 42, 77, 134, 231, 233) Precooling of the face Contact of cold material with the face (water, air, cold packs) Large air/water temperature gradient Increased hypoxia Prolonged or deeper submersion Posture in the water Smaller vital capacity lung volume Previous breath-hold diving experiences A series of repeated apnea dives or apnea exercises Physical fitness Small involuntary breathing movements during the struggle phase of prolonged apnea do not influence the response in the presence of hypoxia and hypercapnia (9). Animal and human experiments have shown that the sympathetic and parasympathetic components of the diving response can be separately influenced by atropine and vasodilators. No chemoreceptor influence comes from acidic, asphyxic blood (203). The sympathetic effects, occurring within 10â€“40 s after cold water touches the face in humans, are affected by input from facial cold-receptors and chemoreceptors. Next comes selective vasoconstriction, with less perfusion measured in the peripheral vascular beds of the skin, muscles, and viscera (9, 77, 102). Metabolism in these organs is decreased, and they shift to anaerobic metabolism, leading to increased lactate. Vasoconstriction causes hypertension (77). Increased carotid artery blood flow and vasodilatation in the brain results in better cerebral perfusion. Brain hypoxia also enhances cerebral perfusion. The result is that the oxygenation of this most oxygen-sensitive organ remains preferentially sustained underwater (38, 126). In addition, the diving response induces, after âˆ¼30 s, vagal-mediated bradycardia. Initially, bradycardia is a baroreceptor response due to vasoconstriction and later a chemoreceptor response due to hypoxia. Bradycardia also results from the decreased cardiac output related to decreased oxygen demand in vasoconstricted tissue. Heart rate can decrease to 30â€“40% of resting levels. During underwater diving competitions, heart rates as low as 20 beats/min have been attributed to the diving response. Bradycardia adds to the oxygen-saving effects through decreased myocardial oxygen consumption (17). The rate-dependent fall in contractility can be counterbalanced by the increase in sympathetic tone. Sometimes ectopic beats occur, either as escape arrhythmias or due to the simultaneous co-activation of the sympathetic and parasympathetic nervous systems. This may result in a vagal cardiac arrest (95, 102, 133). Human studies with experimental head immersion in cold water and during apneic diving have shown that the diving response decreases oxygen consumption, slows arterial desaturation, and prolongs the duration of breath-holding or diving and the duration before asphyxia becomes life-threatening (9, 77, 134, 137). In the context of drowning, some consider the reflex fantastic physiology, others physiological fantasy. Apnea and face immersion in cold water, alone or in combination, may occur in some drowning scenarios. Under these circumstances, the diving response may occur. But many drowning scenarios will involve neither voluntary apnea nor cold water. Other mechanisms may also cause interference. For example, when a drowning victim is able to take a full breath before disappearing under water, the increased intrathoracic pressure may result in decreased cardiac output and hypotension (9). Also, the physical effort associated with the predrowning struggle to maintain the airway clear of the water may significantly decrease

breath-holding and negate the diving response. Bradycardia and hypertension may be indicators that the diving response has been active, information rarely available at the rescue site. Therapeutic interventions at the scene, in the emergency department, and in the intensive care department will limit exploration of the diving response in clinical settings. Despite these reservations, the possibility remains that the diving response has a role in the prevention of fatal drowning, notably in very young children. It is important to realize that not all persons who engage in the struggle of drowning will experience the physiological processes of a diving mammal or human.

Autonomic Conflict Interplay between sympathetic and parasympathetic components of the autonomic nervous system has led to the theory of â€œautonomic conflictâ€• to account for the genesis of cardiac arrhythmias and dysrhythmias (244, 265). Arrhythmias arise due to simultaneous and conflicting positive and negative chronotropic signals to the heart. Human data, and data from isolated hearts, indicate that arrhythmias are most likely to occur in a situation of cyclical vagal stimuli to the heart, for example, with the reinstatement of breathing post-breath-holding, against a background of sympathetic stimulation due to cold, exercise, anger, or anxiety (264) (FIGURE 4). Arrhythmias are usually observed within 10 s of the cessation of breath-holding. The fact that they occur on cold immersion without face immersion (57) indicates that the release of breath-holding is, in itself, an arrhythmogenic trigger, due to neural responses associated with the release of stimulation of the cardiac vagal neurons. The incidence of an arrhythmia increases further if breath-holding is coincident with submersion in cold water (57, 267). This is probably due to the greater vagal drive seen with face immersion and trigeminal nerve stimulation. This is a powerful pro-arrhythmic stimulus that, on initial immersion, occurs at a time when the QT interval does not match the underlying heart rate, further increasing the likelihood of cardiac arrhythmias (286). Cardiac arrhythmias are predominantly supraventricular and junctional but can include short bursts of ventricular tachycardia interposed between periods of bradycardia, supraventricular ectopic beats, or even atrio-ventricular blocks. Arrhythmias tend to occur when heart rhythm changes from tachycardia (sympathetic predominance) to bradycardia (vagal predominance) (57, 267). The appearance of arrhythmias immediately post-breath-holding on immersion in cold water may also depend on the timing or magnitude of this rhythm in relation to the cessation of breath-holding. While autonomic conflict commonly results in arrhythmias, these descend into fatal arrhythmias much less commonly and probably only in the presence of a range of predisposing factors that may include ischemic heart disease, long QT, channelopathies, and atherosclerosis (FIGURE 4) (244). FIGURE 4.Autonomic conflict Cold-water immersion activates two powerful responses: the diving response (on facial immersion) and the cold shock response (on the activation of cutaneous cold receptors). The magnitudes of these responses can vary with a range of factors including water temperature, clothing, and habituation. The diving response triggers a parasympathetically driven bradycardia, whereas cold shock activates a sympathetically

driven tachycardia. It is hypothesized that together these conflicting inputs to the heart can lead to arrhythmias, particularly at the break of breath-hold, which increases parasympathetic tone that varies with respiration. The substrate for arrhythmias is enhanced by various predisposing factors. Figure is from Ref. 244 and used with permission from The Journal of Physiology. Download figureDownload PowerPoint

It is possible that arrhythmias caused by cold water submersion could result in death but go undiagnosed, mainly because electrical disturbances to the heart that result in fatal arrhythmias are undetectable postmortem. Also, even if the primary problem on immersion is cardiac, spontaneous terminal gasping may result in water entering the lungs, giving the appearance of drowning.

Upper Airway Reflexes The upper airway is composed of the nose, pharynx, larynx, and extrathoracic portion of the trachea, and has many reflexes relevant for life, including maintenance of an open airway and airway defense. Mild irritation of the laryngeal mucosa may lead to a laryngeal closure reflex as a protective reflex against materials entering the tracheobronchial tree. Laryngospasm is the closure of the aryepiglottic folds, false vocal cords, and true vocal cords. This reflex responds to direct laryngeal stimulation from secretions, blood, or a foreign body (41, 188â€“190, 285). Other upper-airway reflexes include the pharyngoglottal closure reflex, esophagoglottal closure reflex, and aerodigestive reflex (65, 243). During the drowning process, laryngospasm may prevent the entrance of water into the lungs, but this remains controversial. The existence of laryngospasm, also known as glottis spasm, was mentioned in the earliest drowning studies to explain why 10â€“20% of all dead drowning victims had macroscopically dry lungs (147, 178). Laryngospasm as an explanation for dry lungs seems logical (131). However, dry-drowning and dry-lung have been variably explained not only by laryngospasm but also by vago-vagal cardiac inhibition, pulmonary reflexes, absorption of aspirated fresh water into the circulation, and various reflexes triggered by contact of the body with water (36, 61, 178, 230, 250). Some of these deaths were also labeled â€œhydrocutionâ€• or â€œatypical drowningâ€• in the early medical literature (288). Critical appraisal of the original literature from the 1930s, as well as clinical observations, has concluded that dry-drowning as result of a laryngospasm is nonexistent. If a laryngospasm may initially have occurred, it will cease to operate as a result of progressive hypoxia of the laryngeal muscles while under water breathing efforts are sustained (178, 194). Some morphological forensic studies, also using microscopic tracers of the drowning liquid, indicate that penetration of liquid into the lungs occurs in almost all drowning deaths (148), even in those with macroscopically apparent dry-lung. Actually, dry-lungs with no evidence of liquid penetration can be found only in bodies dumped into water after death on land (148, 178). Mechanisms other than aspiration may, however, also lead to lung changes mimicking liquid aspiration. Case studies describe mild pulmonary

edema after swimming, snorkeling, and diving, especially in cold water (144). Subclinical pulmonary edema has resulted from marginal hyperbaric stress under hypoxic conditions (83), from intense exertion by athletic and military swimmers (144) and from an increase in catecholamines due to hypoxemia and stress, leading to pulmonary vascular overload. Another potential mechanism is negative-pressure pulmonary edema caused by extreme negative intrathoracic pressure from inspiration efforts against a closed glottis (60, 184, 279). On the other side, clinical studies report that the majority of drowning resuscitation survivors, whom can be assumed to have been under water for a sustained interval, have no clinically relevant pulmonary complications (76, 274). One problem in gathering evidence for this debate on upper airway reflexes is that knowledge of laryngeal muscle function is limited. Some information can be extracted from studies on speaking, singing, and swallowing (65, 243, 292). The muscles of the larynx have largely involuntary medulla-mediated tasks during swallowing, breathing, and coughing, and volitional cortex-mediated tasks during speaking and crying for help. For each of its functions, the different vocal-fold movements need rapid and precise control by intrinsic and extrinsic laryngeal muscles. All these muscles can be actively controlled. Older studies assume that the afferent end-organs in the larynx can respond to pressure, flow, respiratory drive, osmolarity, temperature, and chemical irritants (285). More recent studies on the pharyngoglottal closure reflex, relevant for prevention of food aspiration, show that the laryngeal vocal folds close when water is injected rapidly toward the posterior pharyngeal wall (65, 243). Anatomic coordination exists between the larynx muscles, respiratory reflexes, and cough control through stimulation of the same internal branches of the superior laryngeal nerve (8, 242). Because all four functions of the laryngeal muscles (swallowing water, breathing, coughing, crying for help) are relevant to the drowning process, these muscles must play an active but still poorly studied role in drowning (142). Although there is on-going discussion about the existence of laryngospasm during drowning, it will only be protective in those few patients where the spasm has been activated and is still active at the moment of rescue from the water.

Aspiration of Water The lung is an immediately vulnerable target during the drowning process. During laryngospasm, forceful ventilatory movements against a closed glottis may cause mechanical damage. Furthermore, during the drowning process, both hypertonic and hypotonic aspirated liquids cause changes to the pulmonary surfactant and to the alveolocapillary barrier that result in systemic hypoxemia. Confusion exists about the volume of water aspirated in drowning and how these volumes contribute to respiratory impairment. Speculative extrapolations of data from experimental and postmortem studies to clinical settings have contributed to this confusion. Aspirated volumes are also reported in milliliters per pound in some studies and in milliliters per kilogram in others (90, 177, 179, 180). Hypotonic liquid, when reaching the alveoli, damages and dilutes pulmonary surfactant. The increase in the alveolar surface tension, along with diminution of pulmonary compliance, causes alveolar instability and atelectasis that

alters the ventilation-to-perfusion ratio. Because a large part of the lung is not adequately ventilated, more venous blood bypasses the lungs, and the shunt fraction increases. Aspiration of 2.5 ml/kg of sea water causes the pulmonary shunt fraction to increase by 75% (206). Hypotonic fresh water tends to be absorbed into the pulmonary circulation and distributed throughout the body. Aspiration of hypertonic seawater draws liquid from the plasma into the alveoli and also causes damage to surfactant (215). In both situations, the supranormal hydrostatic forces over the alveolar-capillary membrane will disrupt its integrity. Plasma enters the alveoli, incapacitating normal gas exchange. Plasma in the alveoli may also generate foam that further decreases pulmonary efficiency (147). This results in a local adult respiratory distress syndrome-like clinical picture (85, 92, 176, 274). Spontaneous ventilation persists after submersion and causes liquid penetration into the lungs. Moreover, terminal shock induced by a variety of natural causes can produce pulmonary stasis and edema mimicking a wet lung indistinguishable from that observed in actual drowning. It is therefore impossible macroscopically or microscopically to assert whether a lung contains or does not contain aspirated liquid. One way to assess, and eventually quantify, the penetration of drowning liquid into the lungs is to study the presence of microscopic tracers of the drowning liquid (147).

Swallowing of Water Swallowing water during the drowning process may increase the risk for vomiting, spontaneously or during resuscitation, eventually leading to aspiration of gastric content. Swallowing water may also contribute to life-threatening electrolyte disorders. Under normal conditions, the process of swallowing liquid includes an oral phase, a pharyngeal phase, and an esophageal phase (69, 160, 174, 252). Swallowing is triggered by cortical inputs integrated into the swallowing central pattern generator (SCPG) of the brain stem (69, 70, 115, 129, 174). The SCPG sends efferent innervations to over 30 muscles involved in swallowing. Afferent pathways originate from chemical or mechanical receptors in the upper-airway mucosa and from lung and intercostal muscles. Information is conveyed via cranial nerves V, IX, and X to the brain stem and the nucleus tractus solitarium. The main efferent pathways are via the ambiguous and hypoglossal nuclei (XII) (189). Coordination between breathing and swallowing prevents liquid aspiration (189). During swallowing, elevation of the soft palate, tilting of the epiglottis, and SCPG-mediated inhibition of airway reflexes interrupt respiration for 0.5â€“1.5 s during the inspiration-expiration transition or the expiratory phase (37, 63, 127, 190, 205, 240). During drowning, swallowing of liquid usually occurs during partial head-out immersion or during breath-holding (see Sympathetic Activation, Fear of Drowning above). Under these circumstances, active and passive swallowing differ from the normal physiological processes (56). Uncontrolled premature entry of liquid into the pharynx can cause aspiration and swallowing, accentuated by a cough reflex. Stress, increased Pco 2 , decreased Po 2 , respiratory- and lung-volume changes, and unconsciousness hamper coordination between swallowing and respiration may cause swallowing during inspiratory and expiratory phases, with a consequent

risk for aspiration (123, 124, 173, 188â€“190, 223). Water swallowing during drowning has long been a subject of investigation (71, 218), but with little high-quality data. Experiments in the 1970s in rats, when electrolyte disorders were considered important for drowning outcome, suggested that the ratio of aspirated to swallowed liquid differed between fresh (1:1) and salt water (1:3) (58). The relevance of this to conscious humans is unknown. Some authors maintain that drowning victims swallow much more water than they inhale (195). At this moment, autopsy data are still inconclusive (141, 230). Based on one of the author's (P. Lunetta) investigation of over 2,000 fatal drownings, the stomach of a drowning victim is either empty, or contains watery fluid, liquid mixed with food, or exclusively food. Postmortem liquid penetration into the stomach or its leakage into the small intestine impedes reliable prospective studies. Presence of water-borne particles in the stomach, such as plankton, is also not conclusive, because they can penetrate postmortem or can be present in food and beverages consumed before the incident (101, 146, 290). One postmortem computerized tomography (CT) study on 28 retrieved drowning bodies revealed gastric distension in 89%, but high-attenuation sediment in only 21% (135). Another series of 10 fatal fresh-water drowning cases examined by postmortem CT, reported a gastric volume ranging from 50 to 1,200 ml, with an average density of gastric contents less than the control group (49). Although some drowning victims clearly have swallowed water, data are limited as to the incidence and clinical relevance, and whether differences exist between fatal and non-fatal drowning.

Emesis Detailed data on the occurrence of emesis in drowning are also lacking. One study, reported 25â€“60% of drowning victims vomited (151). Another study revealed that emesis occurred in 86% of drowning victims who required cardiopulmonary resuscitation and in 50% of those who required no intervention (154). Autopsy series have disclosed aspiration of gastric contents in 24% of drowning victims (80). In a large series on out-of-hospital cardiac arrest (CA) with a cardiac and non-cardiac etiology, emesis occurred in 30â€“35% of all patients (247). The trigger can be the condition underlying the arrest, CA itself, gastric distension caused by artificial ventilation, or improper chest compression that increases intra-abdominal pressure. The main vagal sensory afferents responsible for emesis originate from mechano-, osmo-, and chemoreceptors activated by gastric distension or mucosal irritation (14, 21). Mucosal chemoreceptors in the stomach can be stimulated by hydrochlorides or hypertonic saline (13). These afferents relay information to the nucleus tractus solitarium and then to the medulla oblongata, where a neural network (central pattern generator) coordinates the efferent response (21, 110). This integration area receives afferents also from the cerebral cortex, the vestibular region, and a chemoreceptor trigger zone located between the medulla and the floor of the fourth ventricle. The chemoreceptor trigger zone detects, within the blood, emetic stimulants, including hypoxia and ketoacidosis. The efferent motor pathways innervate the upper gastrointestinal tract via cranial nerves V, VII,

IX, X, and XII, the diaphragm and abdominal muscles via spinal nerves (21, 26, 110). Emesis includes retroperistaltic activity from the small intestine, relaxation of the pyloric sphincter, downward contraction of the diaphragm with decreased intrathoracic pressure, increase in intra-abdominal pressure, contraction of the abdominal wall muscles, squeezing and contraction of the stomach with elevation of intragastric pressure and closure of the pylorus, relaxation of the esophageal sphincter, and expulsion of gastric contents (130, 172). The extent to which these classical reflex mechanisms explain emesis in drowning is undefined. During drowning, gastric contents can be aspirated into the airways, resulting in pulmonary infection and chemical irritation (68, 274). Emesis can also interfere with pulmonary resuscitation. In drowning, both vomiting and cardiopulmonary resuscitation may cause gastric mucosal tears, the frequency of which varies widely among studies but has been detected in as many as 21% of patients (15, 33, 55, 145).

Electrolyte Disorders Experiments during the 1940s and 1950s have long influenced the concepts of drowning pathophysiology (254â€“256). These experiments stressed the role of liquid osmolarity in drowning, especially the penetration of hypotonic liquid into the circulation, causing hypervolemia, erythrocyte hemolysis, intravascular potassium release, and subsequent VF. Studies beginning during the 1960s (179, 180) suggested that the volume of aspirated water rather than its osmolarity is the critical factor. Pathophysiological differences between freshwater or saltwater drowning are observable in experimental models. However, in most drowning victims, serum electrolyte changes are of limited importance because liquid redistribution within the body rapidly restores electrolyte balance. Hypo- and hypertonic liquid cause a ventilation/perfusion shift and hypoxemia and metabolic acidosis. These, in turn, cause myocardial depression, pulmonary vasoconstriction, and changes in capillary permeability that worsen pulmonary edema (148). The final common pathway is hypoxemia. In most environments, drowning is not associated with clinically important electrolyte changes. When such changes do occur, it can be impossible to disentangle the roles of ingestion and aspiration (136). The small intestine absorbs â‰¥80% of ingested liquid via concentration gradients and complex molecular mechanisms (84). When seawater reaches the small intestine, sodium moves mainly through the jejunal mucosal cells of the villi into capillaries. Water diffusion follows the osmotic gradient (245). In sporadic cases, such as in protracted immersion while wearing a malfunctioning or poorly designed lifejacket, sea-water ingestion following the breath-holding breaking-point directly causes hypernatremia (67). Serum sodium concentrations higher than 145 mM have occurred in pediatric drownings (111). Chlorine ions may also pass the intestinal barrier by concentration gradient, causing metabolic acidosis (67, 111). In specific environments such as the Dead Sea, with its high magnesium and calcium concentration, ingestion of as little as 200 ml may have a significant clinical impact (136). Conversely, swallowing hypotonic liquid thus far has not been reported to result in water intoxication, although swallowing fresh

water can cause hyponatremia, especially in children (287). Electrolyte disorders have been considered a major factor in drowning mortality previously. Current studies suggest that this only occurs in exceptional circumstances.

Reference

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