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Review

The human diving response, its function, and its control

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The purpose of this review is to outline the physiological responses associated with the diving response, its functional significance, and its cardiorespiratory control. This review is separated into four major sections. Section one outlines the diving response and its physiology. Section two provides support for the hypothesis that the primary role of the diving response is the conservation of oxygen. The third section describes how the diving response is controlled and provides a model that illustrates the cardiorespiratory interaction. Finally, the fourth section illustrates potential adaptations that result after regular exposure to an asphyxic environment. The cardiovascular and endocrine responses associated with the diving response and apnea are bradycardia, vasoconstriction, and an increase in secretion of suprarenal catecholamines. These responses require the integration of both the cardiovascular system and the respiratory system. The primary role of the diving response is likely to conserve oxygen for sensitive brain and heart tissue and to lengthen the time before the onset of serious hypoxic damage. We suggest that future research should be focused towards understanding the role of altered ventilatory responses in human breath-hold athletes as well as in patients suffering from sleep-disordered breathing.

A lack of oxygen even for short periods can be detrimental to most birds, mammals, and humans. However, many diving birds, mammals, and humans have adapted to endure hypoxia or anoxia for extended periods (Hermes-Lima & Zenteno-Savin, 2002). The major physiological adaptation allowing animals to endure the lack of oxygen during apnea is the diving response. The diving response has been demonstrated across a variety of diving birds, mammals (Butler & Jones, 1997), and humans (Hong, 1989). It is qualitatively similar between species and involves both bradycardia and peripheral vasoconstriction triggered in response to respiratory arrest (Daly, 1997) and stimulation of facial cold receptors (Elsner & Gooden, 1983). For the purpose of this review, we will use the following terms: diving response, apnea, and face immersion and define them as follows. The diving response is a reduction in heart rate because of an increase in cardiac parasympathetic nerve activity, peripheral vasoconstriction on the arterial vascular tree, and an increase in sympathetic activity triggered in response to the cessation of respiration and, but not necessarily including, the stimulation of facial cold receptors. We will refer to the cessation of respiration as apnea and the stimulation of facial cold receptors by water will be referred to as face immersion.

The human diving response involves bradycardia (Asmussen & Kristiansson, 1968), vasoconstriction of selected vascular beds (Leuenberger, et al. 2001), reduced blood flow to peripheral capillary beds (Elsner, Gooden, Robinson, 1971), and increased sympathetic outflow to the periphery (Leuenberger et al., 2001). The heart rate of human breath-hold divers can drop to 20–30 b.p.m. while diving (Ferrigno et al., 1997). Their arterial blood pressure is not maintained and can dramatically increase to values as high as 280/200 mmHg (systolic/diastolic) (Ferrigno et al., 1997). Recent evidence suggests that an active contraction of the spleen is also a characteristic of the human diving response (Hurford et al., 1990). This concept of splenic contraction is based on hematological observation (Schagatay, et al. 2001), radionuclide measurements (Espersen, et al. 2002), and ultrasonic measurements of spleen volume (Bakovic et al., 2003). The diving response elicited in diving mammals is quite similar to that of the humans; however, diving mammals are claimed to be able to maintain their mean arterial pressure (MAP) while humans cannot. In the Weddell seal it is not uncommon to observe not only a decrease in heart rate of 40 b.p.m. and a drop in cardiac output ($\dot{Q}$) from 40 to 6 liters but also a mean blood pressure of 120 mmHg maintained by an intense peripheral vasoconstriction (Hochachka, 1981). Apnea alone is sufficient to trigger the diving response; however, when coupled with stimulation of facial cold receptors, as with face immersion, a greater response is

Table 1. Studies describing the percent change in heart rate (HR), arterial oxygen saturation (SaO_2), and mean arterial pressure (MAP) in subjects exercising under either apneic conditions or apnea and face immersion for the given apneic time and workload

	Apneic time (s)*	Workload (W)	Apneic LV	HR (%)	SaO_2 (%)	MAP (%)
Apnea						
Andersson et al. (2004)	40	80	80% VC	−25	−8	28
Lindholm et al. (2002)	Maximal (40)	100	60% VC	−40	−20 to 50	50
Andersson et al. (2002)	30	100	80% VC	−21	−7	34
Lindholm et al. (1999)	30	120	RV+3.5 L	−31	−15	44
Apnea and face immersion						
Andersson et al. (2004)	40	80	80% VC	−35	−6	33
Andersson et al. (2002)	30	100	80% VC	−33	−5	42

The lung volume (LV) at which apnea was initiated is not identical in all studies. RV, residual volume.
*Apneic times contained within brackets refer to the average apneic time.

seen (Stromme et al. 1970; Schuitema & Holm, 1988). Table 1 summarizes the change in heart rate, the change in arterial oxygen saturation (SaO_2), and the change in MAP in exercising humans initiating the diving response with apnea alone or with apnea plus face immersion. The change in heart rate under apneic conditions is strongly influenced by the held lung volume and will be described in detail in the section on lung volume.

This review will focus on the human diving response, its function, and its control with an emphasis on the most recent studies. As described, a number of exquisite physiological changes are associated with apnea, face immersion, and the diving response. This review will address the primary role of the diving response and the control of the cardiovascular responses that are associated with apnea, apnea and face immersion, and the diving response.

Role of the diving response

What is the primary role of the human diving response? Some investigators suggest evidence of an oxygen (O_2)-conserving effect of the diving response (Wolf et al., 1965; Andersson & Schagatay, 1998a; Lindholm et al., 1999; Ferretti, 2001; Andersson et al., 2002), whereas others do not (Craig & Medd, 1968; Hong et al., 1971). This section will provide support for an O_2-conserving role of the diving response and is a preface to the subsequent section, which describes the diving response cardiorespiratory control mechanisms.

The human diving response potentially conserves O_2 in several ways. Both an intense vasoconstriction of peripheral and visceral capillary beds and a reduction in $\dot{Q}$ reduce oxygen consumption ($\dot{V}O_2$) in the periphery and of the viscera and spare O_2 for oxygen-sensitive tissues, such as the brain and the heart (Elsner & Gooden, 1983). Bradycardia could also serve to reduce the O_2 requirements of the myocardium, thus conserving blood O_2 stores (Daly, 1997). The plasma lactate concentration is increased from control after apnea in air and even more so after apnea with face immersion, suggesting a greater reliance on anaerobic metabolism during apneas (Andersson et al., 2004). Individuals who have had 7–10 years of breath-hold diving experience have reduced post-apnea blood acidosis and oxidative stress (Joulia et al., 2002). Also, as suggested by Ferretti (2001), a reduced basal metabolic rate may also serve as an O_2-conserving mechanism. In support of this hypothesis is the Ama, a group of commercial divers who harvest shellfish and perform frequent breath-hold dives each working day. They have been characterized as having reduced basal metabolic rates (Kang et al., 1965). However, more recent studies on the Ama population have been unable to detect a reduced basal metabolic rate (Ferretti, 2001). This discrepancy can in part be explained by the fact that present-day Amas use modern wetsuits and have less subcutaneous fat while the earlier Amas used cotton suits (Hong et al., 1986). Subcutaneous fat provides insulation and reduces heat loss to the surroundings thereby reducing the basal metabolic rate. This suggests that the O_2-conserving effect of having a reduced basal metabolic rate may be unrelated to the diving response and may be related to thermal acclimatization.

Increased carotid artery blood flow is consistent with the hypothesis that blood flow is redistributed from peripheral circulation to cerebral circulation (Pan et al., 1997). A reduction in skin blood flow during simulated dives in trained breath-hold divers indicates a vasoconstriction in peripheral capillary beds (Andersson et al., 2002).

While average apneic $\dot{V}O_2$ can be quantified rather easily it is still difficult to quantify $\dot{V}O_2$ during the time course of an apnea; indirect estimates of $\dot{V}O_2$ must be made. These estimates are based on SaO_2 and on respired partial pressures of oxygen (PO_2). Using these methods, studies have shown that an O_2-conserving effect is present by demonstrating that

$\dot{V}O_2$ from the lungs is temporarily postponed (Lindholm et al., 1999; Lindholm & Linnarsson, 2002) and that arterial desaturation is slowed (Andersson & Schagatay, 1998a; Andersson et al., 2002), thus prolonging the duration of time required before asphyxia reaches a life-threatening condition. During diving, however, the increasing ambient pressure with increasing depth further complicates the ability to calculate $\dot{V}O_2$, gas pressures, and SaO_2. The increase in pressure that results when diving to depth results in a hyperoxic state during descent as the alveolar PO_2 is increased and the alveolar arterial O_2 difference is widened (Liner et al., 1993). However, upon ascent the release of pressure on the thoracic cavity results in a reduction in alveolar PO_2, which may lead to a reversal of flow of O_2 (Liner et al., 1993). This can cause the arterial PO_2 to be rapidly reduced to life-threatening levels and the risk of the loss of consciousness during ascent is increased (Ferretti, 2001). Liner and Linnarsson (1994) studied the rate of metabolic recovery following a simple surface breath-hold and following a breath-hold dive simulated within a pressure chamber. In this study, the time constant for recovery of CO_2 and ventilation were increased following a simulated breath-hold dive but, the rate of O_2 consumption was not different.

Water immersion itself has a profound effect on blood distribution and $\dot{V}O_2$ in exercising humans. The hydrostatic counter-pressure occurring with water immersion causes an increase in $\dot{Q}$, central blood volume, and pulmonary arterial pressure (Choukroun & Marene, 1990). Central hypervolemia occurring with water immersion results in a delayed $\dot{V}O_2$ response to exercise (Hayashi & Yoshida, 1999). Hayashi and Yoshida (1999) indicate that $\dot{V}O_2$ is delayed in head-out water immersion exercise because of either a greater muscle O_2 store or an alteration in the distribution of blood to working muscles. Subjects were studied at a water temperature of 30–32 °C and an air temperature of 22–25 °C. Therefore, water immersion itself may initially have an O_2-conserving effect by increasing the O_2 supply to the intrathoracic region and limiting supply to the periphery.

Recently, Lindholm et al. (1999) studied nine men, seven of whom had breath-holding experience, during apneic exercise and exercise with rebreathing, two conditions that produce an asphyxic stimulus; however, bradycardia was present only under conditions of apnea. The rate of decline in SaO_2 was reduced and the PO_2 was higher at the end of apnea compared with the end of rebreathing. Furthermore, those individuals with the most prominent bradycardic responses had the slowest decline in SaO_2. The difference between these two cardiovascular responses indicates that a significant O_2-conserving effect is triggered by apnea and not asphyxia.

Stimulation of facial cold receptors by cold water augments the human diving response and elicits a greater degree of bradycardia, reduction in blood flow, and hypertension (Andersson et al., 2000). Apnea with face immersion results in a 25% reduction in heart rate while apnea without face immersion results in only a 10% reduction in heart rate (Andersson et al., 2000). By examining the cardiovascular responses to dry breath-holds and face immersion breath-holds during a 100 W cycle exercise in trained breath-hold divers, Andersson et al. (2002) determined that a more pronounced diving response elicited by face immersion provides a reduction in the rate of decline in arterial O_2 desaturation and an associated O_2-conserving effect during exercise. Results obtained from Lindholm, Nordh and Linnarsson (2002) provide further support when eleven male subjects underwent 100 W cycle exercise with repeated apneas performed with air or a helium–O_2 mixture (95% O_2–5% He). Their study showed that the reduced carotid chemoreceptor stimulation with hyperoxia results in a smaller reduction in end-apneic heart rate and in end-apneic MAP than with air. Cardiovascular responses still occurred under hyperoxic conditions but arterial desaturation did not occur. Subjects with previous breath-hold diving experience when asked to breath-hold for a maximal duration held their breaths longer when the diving response was augmented by face immersion; this was not true for untrained subjects (Schagatay & Andersson, 1998). Similar results were found in earlier studies and have been ascribed to psychological factors (Mukhtar & Patrick, 1986; Sterba & Lundgren, 1988).

Lindholm and Linnarson (2002) observed a lower pulmonary O_2 uptake than predicted if the $\dot{Q}$ and venous O_2 saturation remained constant during the apneic period. This indicates that the cardiovascular responses to apnea (i.e. the diving response) play a significant role in slowing O_2 uptake from the lung to the blood and, therefore, conserving the lung O_2 store.

The concept of splenic contraction has recently been described as a property of the human diving response (Hurford et al., 1990; Schagatay et al., 2001; Espersen et al., 2002; Bakovic et al., 2003) and, as seen in intermittent hypoxia studies, may play an O_2-conserving role (Kuwahira et al., 1999, 2000). The spleen serves as a dynamic erythrocyte blood cell reservoir that contracts and releases significant volume of erythrocytes during increased activity (Stewart et al., 2003), diving (Espersen et al., 2002), or in response to severe hypoxia (Hoka et al. 1989). Splenic contraction is induced by a catecholamine-mediated α_2-adrenoreceptor response (Kuwahira et al., 1999). Since contraction of the spleen increases hematocrit and hemoglobin circulating in the blood,

then it would be expected that O_2 transport would also be enhanced. Schagatay et al. (2001) studied subjects with intact spleens and subjects who had undergone a splenectomy. Subjects performed five maximal apneas with face immersion, and hemoglobin and hematocrit concentrations were measured. Subjects with intact spleens had a 6.4% increase in hematocrit and a 3.3% increase in hemoglobin concentration. There was no change in these parameters in splenectomized subjects. Also, subjects with intact spleens showed a 54% increase in the maximal apneic duration. This suggests that splenic contraction occurs in humans and may prolong repeated apneas. Espersen et al. (2002) used an erythrocyte radiolabelling technique with scintigraphic measuring to determine the extent of splenic contraction in subjects with and without diving experience. Under the condition of ''maximal simulated diving'', the relative splenic area was reduced by 30–40% and the relative content of splenic erythrocytes was reduced by about 34%. These findings were not related to previous diving experience. Hemoglobin and hematocrit concentrations increased by 0.3 mmol/L and 1%, respectively. Bakovic et al. (2003) made two-dimensional ultrasonic measurements of spleen volume and blood flows to repeated apneas. The blood flow in the splenic artery and splenic vein was not affected by breath holding; however, the spleen volume decreased by approximately 20% after the first apnea and was only partially recovered 60 min after the last apnea. Rapid spleen contraction and its slow recovery might contribute to the prolongation of repeated apnea attempts. The results presented show that splenic contraction does indeed occur and may be responsible for the concurrent increase in hemoglobin and hematocrit concentration. Unfortunately, more research needs to be conducted before we can conclusively determine the role of splenic contraction as one of O_2 conservation; however, the hypothesis seems reasonable.

The studies presented above provide evidence of a strong O_2-conserving role for the diving response. The diving response slows O_2 uptake from the lung and reduces the rate of arterial blood desaturation, thus slowing the depletion of both lung and blood O_2 stores. The diving response preferentially perfuses the brain and reduces the delivery of O_2 to peripheral capillary beds by slowing blood flow with a tight vasoconstriction.

Control of cardiovascular responses

Apnea can result by two different mechanisms. Firstly, apnea can occur voluntarily; in this situation, a person consciously inhibits the respiratory centers via a centrally induced pathway. Apnea occurring in this way includes simple breath holding, the type of apnea occurring in breath-hold divers. Secondly, apnea can result in a reflexive manner by involving stimulation of receptors that provide afferent information indicating airway obstruction and, therefore, eliciting inhibition of the respiratory centers. Apnea can occur in this way by several mechanisms, including face immersion, upper airway irrigation, and airway obstruction. Reflexive apnea occurs during conditions of forced or accidental submersion (Gooden, 1994) and obstructive sleep apnea syndrome (Kohnlein et al., 2002; Veasey, 2003; Wolk & Somers, 2003).

A complex neural network integrating the respiratory and cardiovascular systems controls the diving response. This review has focused on the human diving response; however, because of the difficulty in studying control schematics in humans, some results from animal research will be provided in this section to complement existing human studies. The basic control model is illustrated in Fig. 1. Like any model of control, the system has inputs that interact with major central nervous system centers to activate the output or response of the system. In our model, the inputs are facial cold receptors, carotid chemoreceptors, baroreceptors, pulmonary stretch receptors, and atrial receptors. These inputs all project to the nucleus tractus solitarius (NTS), branch, and then continue on to one of three central nervous system centers: the respiratory center, the cardiac parasympathetic center, or the vasomotor center. In response to apnea, which acts as a ''master switch'', the above receptors interact in the NTS and project to either inhibit or excite their respective control center and thus produce the cardiovascular responses associated with the diving response.

Face immersion

Direct contact of water on the forehead, eyes, and nose is a potent stimulus for eliciting the diving response (Schuitema & Holm, 1988; Daly, 1997). These areas are supplied by the trigeminal nerve where stimulation causes inhibition of respiration and excitation of vasomotor centers and cardiac vagal motoneurones (Elsner & Gooden, 1983). These cardiovascular responses potentiate the diving response by further reducing the heart rate and vasoconstriction occurring during a dry breath-hold (Andersson et al., 2002). Facial cold receptors are more strongly excited by immersion in water with a reduced temperature (10–15 °C) (Daly, 1997); varying the temperature between 15 and 35 °C has little effect (Asmussen & Kristiansson, 1968; Mukhtar & Patrick, 1986). More recently, it has been shown that the temperature of ambient air may also be important in determining how water temperature augments

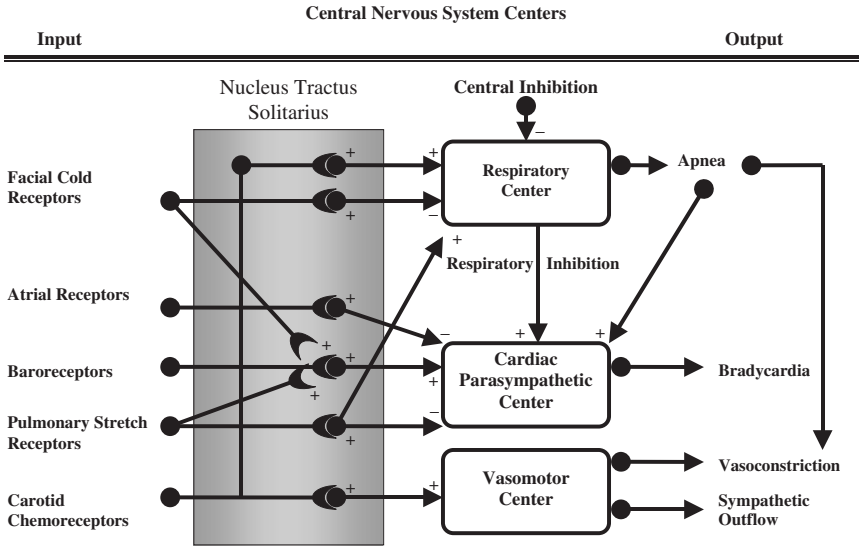

Fig. 1. The basic diving response control schematic. Inputs appear on the left, outputs are displayed on the right, and in between are the neural connections located in the nucleus tractus solitarius and in the central nervous system control centers. Excitatory neural connections are indicated by a "+" sign. Inhibitory neural connections are indicated by a "–" sign.

the diving bradycardia (Schagatay & Holm, 1996). In this study by Schagatay and Holm (1996), subjects' faces were immersed in water at a temperature of 10 and 20 °C while the ambient air temperature was 30 °C; the results showed that a water temperature of 20 °C also augments diving bradycardia at warmer air temperatures. Occurring together, apnea, face immersion in water, and cold exposure have a synergistic effect on diving bradycardia, which is greater than the sum of each individual response (Marsh et al., 1995).

During eupnea, face immersion results in a small reduction in heart rate; however, the full effects of the diving response will not be observed without cessation of respiration (Asmussen & Kristiansson, 1968; Andersson et al., 2000). This small reduction in heart rate is also seen in ducks breathing through a tracheostoma while their heads are immersed in water (Rey, 1971). Stimulation of receptors of the forearm with cold water does not result in bradycardia; in fact, the heart rate increases, which is likely because of an inhibition of parasympathetic activity and increases in the β-adrenergic sympathetic activity to the heart (Andersson et al., 2000). Therefore, the diving response is enhanced by stimulation of facial cold receptors, and not skin receptors in other regions of the body.

Cardiac parasympathetic activity, assessed by heart rate variability, increases during face immersion and even during head-out water immersion (Hayashi et al., 1997; Perini et al., 1998). The diving response has a functional property for conserving O_2. Since O_2 delivery is not interrupted during breathing, it seems appropriate that the diving response be inhibited during eupnea. Stimulation of facial cold receptors accentuates the diving response but is not a required stimulus for initiating the diving response (Asmussen & Kristiansson, 1968).

Recently, results from a study by Journeay, Reardon and Kenny (2003) suggest that it is possible to alter the cardiac parasympathetic response during facial immersion by altering cardiac filling. In this study the diving bradycardic response was attenuated when venous return was inhibited by applying lower body negative pressure and accentuated by applying lower body positive pressure. This study also showed that the cardiac parasympathetic response can be attenuated by inducing a mild hypotension through exercise. Peripheral blood flow and MAP did not change between conditions, suggesting that, during facial immersion, cardiac and peripheral responses are exerted separately.

Chemoreceptor stimulation

The human carotid body serves the primary purposes of detecting and eliciting a response to hypoxia and maintaining arterial blood pH and the partial pressure of carbon dioxide ($PaCO_2$) (Donnelly, 1997). The carotid body responds to chemical stimuli by increasing activity in the carotid sinus nerve. The carotid body is composed of two essential elements combined with a carotid sinus nerve afferent: (1) type I cells, or glomus cells, which are chemosensitive, and (2) type II cells that play a supportive glial-like role (Gauda, 2002). It is proposed that hypoxia leads to glomus cell depolarization by inhibiting an O_2-sensitive potassium channel (Donnelly, 1997).

Animal studies have shown that the primary cardiovascular responses to stimulation of the carotid body by intracarotid injection of a chemical agent or by a sustained stimulus provided by hypoxic blood in a vascularly isolated perfused carotid body preparation are: bradycardia, vasoconstriction, and an increased secretion of suprarenal catecholamines (Daly, 1997). These reflexive responses are inhibited

by activity arising from slowly adapting pulmonary stretch receptors (Angell-James et al., 1981) and central respiratory neuronal drive (Whitelaw et al., 1981; Mukhtar & Patrick, 1986). Pulmonary stretch receptors prevent inputs from the carotid chemoreceptors from increasing not only cardiac vagal motoneuron activity (Gross et al., 1976) but also sympathetic outflow in the periphery. In the presence of these secondary respiratory mechanisms, carotid body stimulation results in an increase in ventilation, tachycardia, and vasodilation; the primary cardiovascular responses are suppressed (Angell-James & Daly, 1969; Daly, 1997). However, under the conditions of apnea, with respiration ceasing at functional residual capacity, the secondary respiratory mechanisms are suppressed and full expression of the cardiovascular effects of excitation of the carotid bodies can be observed (Daly, 1997).

The cardiovascular responses characterized by the diving response are triggered solely by respiratory arrest and are independent of chemoreceptor stimulation by asphyxic blood. The diving response is still elicited after hyperventilating with 100% O_2 but it is accentuated by asphyxic blood (Elsner et al., 1971). However, chemoreceptor tone appears to be important for the development of diving bradycardia as denervation of the arterial chemoreceptors eliminates most of the heart rate response in ducks (Jones & Purves, 1970). Also, as seen in carotid body resected asthmatics, tachycardia occurs with breath holding (Gross et al., 1976). Stimulation of chemoreceptors in the duck by intravenous cyanide injection produces an increase in blood pressure, occurring concomitantly with vasoconstriction (Vacca et al., 1977). Hypoxia is an important chemoreceptor stimulus for the development and maintenance of diving bradycardia in humans, and hypercapnia may actually attenuate the diving bradycardic response (Lin et al., 1983).

Effects of lung volume

The diving response is modulated by activity arising in afferents of slowly adapting pulmonary stretch receptors. Specifically, the cardiovascular reflexes that occur in response to apneic asphyxia are attenuated or abolished by excitation of slowly adapting pulmonary stretch receptors (Angell-James & Daly, 1969). It is thought that this response arises through a mechanism similar to that resulting from respiratory sinus arrhythmia. With this phenomenon, heart rate increases during inspiration because of parasympathetic withdrawal and decreases during expiration with an increase in parasympathetic tone (Daly, 1997). This respiratory sinus arrhythmia heart rate response is dependent upon vagal nerve integrity (Angell-James et al., 1981).

The diving response is affected by intrapleural pressure and lung volume. Heart rate is less for any given intrapleural pressure, the larger the lung volume, and bradycardia is greatest at larger lung volumes (Song et al., 1969). However, these results contradict more current research with animals and humans, which clearly shows that the bradycardic response is greatest with smaller lung volumes (Angell-James et al., 1981; Daly, 1997; Andersson & Schagatay, 1998b). In seals, a close relationship exists between lung volume and output from vagal afferent nerve fibers that innervate pulmonary stretch receptors (Angell-James et al., 1981). During diving, a decrease in pulmonary stretch receptor activity is an important mechanism for the development of diving bradycardia. In dogs, spontaneous lung movements override diving bradycardia (Angell-James & Daly, 1969). In human breath-hold divers, under simulated diving conditions, the heart rate decreases more when the lung volume is held at 60% in comparison with 85% of vital capacity (Andersson & Schagatay, 1998b). Potentially this occurs because, at smaller lung volumes, activity in slowly adapting pulmonary stretch receptors is minimal or absent. It can further be speculated that, at greater lung volumes, high intrathoracic pressures inhibit venous return and reduce stroke volume that in part will be compensated by an increased heart rate (Ray & Saito, 2000). Respiratory arrest occurring at smaller lung volumes will result in greater arterial chemoreceptor stimulation by hypoxia because of a reduced lung O_2 store and will further accentuate diving bradycardia.

Lung volumes (Seals et al., 1990) and respiratory phases (Seals et al., 1993; St. Croix et al., 1999) also have an effect on the sympathetic outflow to the periphery that is independent of respiratory motor output. In spontaneously breathing humans muscle sympathetic nerve activity (MSNA) bursts are maximal at end-expiration and at a minimum at end-inspiration (St. Croix et al., 1999). Respiratory motor output can be changed with several methods: (1) passive positive pressure mechanical ventilation, (2) voluntary hyperventilation, (3) assisted mechanical ventilation, and (4) inspiratory resistance with no effect on the amplitude of the MSNA bursts (Seals et al., 1993; St. Croix et al., 1999). Khayat et al. (2004) studied the role of sensory input from the lungs in its control of MSNA during and after apnea in healthy neurally intact humans and bilateral lung transplant patients. The temporal pattern and the peak increase in MSNA were similar between groups during apnea; however, the MSNA present in the first 5 s after resumption of breathing was greater in the lung transplant patients. Thus, pulmonary vagal afferent input, activated by post-apnea hyperventilation, does contribute to the prompt suppression of MSNA below baseline immediately post-apnea but does

not contribute to sympathetic excitation during apnea.

Respiratory neuronal drive

The drive to breathe affects diving bradycardia in a manner similar to that of pulmonary stretch receptors. Central respiratory drive inhibits carotid body activity from exciting cardiac vagal motoneurones (Elsner & Gooden, 1983; Gooden, 1994).

Through an unknown mechanism, breath holding acts as a stimulus to increase respiratory neural drive (Whitelaw et al., 1981). One hypothesis involves excitation of the central nervous system by the lack of feedback from pulmonary stretch receptors and respiratory muscle spindle afferents (Whitelaw et al., 1981). Secondly, chemoreceptor stimulation by the progressing asphyxia increases the ensuing urge to breathe. However, face immersion in cold water reduces the ventilatory drive in humans (Mukhtar & Patrick, 1986). Eventually, the drive to breathe becomes too much to ignore and involuntary respiratory contractions begin to occur (Whitelaw et al., 1981). Breathing is avoided by tightly contracting the glottis and thus closure of the upper airway. The breath-hold breakpoint is said to occur at the point when involuntary respiratory movements begin to occur (Whitelaw et al., 1981).

Sympathetic nerve activity

Increased muscle sympathetic vasomotor nerve activity tightly constricts intramuscular vessels and dermal vessels, resulting in increased resistance to blood flow and blood pressure. Normally, a close relationship between blood pressure and MSNA exists and is governed primarily by inhibitory baroreceptors' input but, during diving, facial cold receptor input and chemoreceptor input also modulate sympathetic nerve activity (Somers et al., 1991). Sympathetic nerve activity, which can be recorded directly from peripheral nerves in humans using the microneurography technique, has different properties depending upon where it is being recorded. Increased MSNA represents a vasoconstrictor response in vessels supplying muscle tissue while increased skin sympathetic nerve activity (SSNA) primarily represents vasoconstriction in response to thermoregulation but is also activated by stress (Fagius & Sundlöf, 1986).

Facial cold receptor activity provides an important stimulus for triggering MSNA that is greatest when facial cold receptors are stimulated by cold water (9 °C) and least when stimulated by 34 °C water (Fagius & Sundlöf, 1986). Apnea without face immersion results in a small increase in bursting rate and amplitude of MSNA; however, the response is greatest when face immersion and apnea occur together (Fagius & Sundlöf, 1986).

Fagius and Sundlöf (1986) showed that SSNA increases in anticipation of the dive and is either maintained throughout it or, in some cases, inhibited. SSNA is unaffected by face immersion and water temperature. More recently, Fagius and Traversa (1994) have provided data confirming that SSNA is unaffected by water temperature and dive duration; however, these researchers did observe a sudden reduction in SSNA upon face immersion, indicating vasodilation and increased skin blood flow. Differences between the two studies are likely a result of the different nerves recorded; Fagius and Sundlöf (1986) recorded from the peroneal nerve while Fagius & Traversa (1994) recorded from the median nerve which innervates glabrous skin of the hand.

Chemoreceptor input also appears to be an important cause for modulating the vasoconstrictor response and exciting muscle sympathetic nerves. Both hypoxia and hypercapnia increase both MSNA and MAP (Somers et al., 1991; Xie et al., 2000; Leuenberger et al., 2001). Normally, a tight interaction between arterial baroreceptors and peripheral chemoreceptors regulates sympathetic nerve activity and blood pressure in humans. Pharmacologically increasing blood pressure with phenylephrine inhibits the sympatho-excitatory response to stimulation of peripheral chemoreceptors with hypoxia, but not during hypercapnia (Somers et al., 1991). These findings seem to illustrate an uncoupling of the baroreceptor–chemoreceptor response resulting in an elevation of the MAP during apnea. Altering arterial blood gas tensions before a breath-holding period alters chemoreceptor stimulation and alters the MSNA response. Breath-holding with 10% O_2 results in greater MSNA activity and MAP than breath-holding on 100% O_2 or room air (Leuenberger et al., 2001).

The above evidence suggests that sympathetic nerve activity and the vasoconstrictor response are affected by inputs from facial cold receptors, chemoreceptors, and baroreceptors but are unaffected by pulmonary stretch receptors.

Asphyxia and chemosensitivity

With apnea, progressive arterial hypoxemia and hypercapnia occur. All healthy people who voluntarily engage in breath-holding activities are regularly faced with the threat of asphyxia and display adaptations that enable longer breath-hold durations and a more pronounced diving response. Non-divers can generally reduce their arterial partial pressure of oxygen (PaO_2) as low as 60 mmHg and their partial pressure of carbon dioxide ($PaCO_2$) as high as 45 mmHg; yet, trained breath-hold divers will endure

a breath-hold until PaO_2 has fallen to 35 mmHg and $PaCO_2$ has increased to 50 mmHg (Ferretti, 2001). Trained synchronized swimmers can sustain a normoxic breath-hold for approximately 109 s while non-diving controls can only breath-hold for 69 s on average (Bjurstrom & Schoene, 1987). After 2 weeks of daily apneic training, the diving response is increased and the duration of breath-hold is increased (Schagatay et al., 2000). It is hypothesized that those regularly participating in breath-holding activities have a reduced chemosensitivity to progressive hypoxia and hypercapnia and that the resultant decrease in respiratory drive increases the magnitude of the cardiovascular responses and enables longer breath-hold times. However, it should be noted that not all individuals involved in breath-holding activities are faced with the same stimuli. Breath-hold divers who dive to depth are faced with hyperoxic hypercapnia for a major portion of the dive as hydrostatic pressures are transmitted to alveolar gases (Ferretti, 2001). On the other hand, individuals who remain at sea level or near the surface are more likely to face conditions of hypoxic hypercapnia.

Those with sleep-disordered breathing, like those who voluntarily engage in breath holding at sea level, are regularly faced with hypoxemia and hypercapnia. These subjects with sleep apnea have recurrent episodes (15–30+) of respiratory airflow cessation during sleep lasting 30–60 s (Kohnlein et al., 2002). Altered autonomic function has been determined to result in subjects suffering from sleep apnea and is associated with adverse affects. Those with sleep apnea have chronically elevated sympathetic activity (Spicuzza et al., 2002) and, consequently, increased peripheral resistance and blood pressure (Wolk & Somers, 2003).

Reduced chemosensitivity to progressive hypoxia and hypercapnia has been observed in a variety of athletes including breath-hold athletes and elite endurance athletes. Reduced chemosensitivity is also described in sleep apnea patients. Both a reduced hypoxic ventilatory response and a hypercapnic ventilatory response have been described in sleep apnea patients (Garcia-Rio et al., 2002). A reduced hypoxic ventilatory response has been observed in the Japanese Ama (Masuda et al., 1981) and synchronized swimmers (Bjurstrom & Schoene, 1987) while the hypercapnic ventilatory response was not different from that of the controls. Other studies, however, describe a reduced ventilatory response to hypercapnia in underwater hockey players (Davis et al., 1987), elite breath-hold divers (Grassi et al., 1994), and in trained divers (Delapille et al., 2001) but not a reduced hypoxic ventilatory response (Grassi et al., 1994). The discrepancies in the above studies are likely associated with differences in the condition faced (i.e. hypoxic hypercapnia vs hyperoxic hypercapnia), gender differences in ventilatory control (i.e. failure to control for progesterone fluctuations occurring naturally with the female menstrual cycle), and differences in methods for measuring chemosensitivity (i.e. steady-state method vs progressive method).

Human breath-hold divers have a blunted ventilatory drive. This response perhaps represents an adaptation that provides them with a greater O_2-conserving effect and the ability to withstand asphyxia for longer durations. It is, however, unclear whether chronic episodes of hypoxemia and hypercapnia result in an altered resting sympathetic tone and elevated blood pressure in this healthy population of divers, as is seen in patients with sleep apnea. Xie et al. (2000) exposed healthy humans to intermittent asphyxia and found that sympathetic nerve activity increased progressively over the 20 min series and remained elevated for at least 20 min after removal of the chemical stimuli.

Perspectives

The human diving response involves bradycardia, vasoconstriction, a reduction in blood flow, and an increase in the sympathetic outflow to the periphery. Recently, splenic contraction has been shown to occur in humans and likely plays a role in supplying additional O_2-rich blood to the vital organs of the body (Schagatay et al., 2001; Espersen et al., 2002; Bakovic et al., 2003). The diving response serves the purpose of preserving life. Under conditions where respiration ceases and the face becomes submerged, the diving response is initiated. Total body $\dot{V}O_2$ becomes reduced to provide O_2 for the heart and the brain. This response is greater in individuals who have experience in breath-hold diving and apnea (Schagatay & Andersson, 1998). Several recent publications have studied the diving response during the condition of physical work (Lindholm et al., 1999; Andersson et al., 2002; Lindholm & Linnarsson, 2002; Lindholm et al., 2002; Andersson et al., 2004). In humans, an adaptation to breath holding is a reduction in the chemical drive to breathe. It is unclear as to whether or not a reduction in the hypoxic ventilatory response and the hypercapnic ventilatory response would be advantageous to the breath-holding athlete from a safety point of view. Future research needs to be conducted to determine the role of the altered ventilatory responses in the human breath-hold athlete; comparisons with those patients with sleep-disordered breathing are indeed required.

Key words: asphyxia, apnea, bradycardia, breath-hold diving.

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