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The trigemino-cardiac reflex in adults: own experience

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"By systematic observation, the incidence of the trigemino-cardiac reflex during neurosurgical procedures around the trigeminal nerve was shown to be approximately 10–18%…"

The trigemino-cardiac reflex

The trigemino-cardiac reflex (TCR) has previously been described in the literature as a reflexive response composed of bradycardia, hypotension and gastric hypermotility seen upon mechanical stimulation anywhere in the distribution of the trigeminal nerve [1–5]. Based on the initial rabbit neurostimulation experiments of Kumada *et al.* in 1977 [6], TCR was first observed by Schaller *et al.* in 1999 during neurosurgical operations [5]. By systematic observation, the incidence of the TCR during neurosurgical procedures around the trigeminal nerve was shown to be approximately 10–18%, independently of the surgeon who operated or the approach that was used [3,7–12]. In their key works, Schaller *et al.* first defined TCR in detail, and their observations are at present generally accepted [3,5,13–15].

The diving reflex

The diving reflex (DR) in humans is characterized by breath-holding, slowing of the heart rate (HR), decreased cardiac output, peripheral vasoconstriction and increased mean arterial blood pressure (MABP) [16]. The DR in humans may be modified by various factors, the most important of which include water temperature, exercise, partial arterial oxygen and carbon dioxide tension and psychological factors [16].

Overview

Although both reflexes share many similarities, their relationship and especially their functional purpose in humans has not yet been clearly defined. In this article, we have tried to integrate these two phenomena into a unified physiological concept. We hypothesize that the TCR and DR are closely linked functionally, representing phylogenetically old reflexes. Both reflexes are of physiological importance during the first months of human life.

General similarities

There are obvious strong links between TCR and DR that are generally accepted: both reflexes are based on the integrity of the TCR's brain stem reflex arc [3,11]. In both TCR and DR, the bradycardia response is induced via reflex centers located in the medulla oblongata [5,17]. Efferent parasympathetic pathways mediate bradycardia; efferent sympathetic pathways mediate peripheral vasoconstriction.

"There are obvious strong links between the trigemino-cardiac reflex and the diving reflex that are generally accepted…"

General differences

The trigemino-cardiac reflex occurs either after peripheral or central stimulation of the trigeminal nerve [3]. DR is seemingly nothing other than a peripheral TCR [4]. What differs is that in TCR there is a MABP decrease, whereas in DR the MABP gradually increases. Presently, it is unclear whether this MABP increase is specific for all peripheral TCRs or only for a single subgroup [3,18].

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Differences in bradycardia

It is well-known that diving bradycardia in man is reduced while taking a breath, even though the inspired gas does not alter the blood gas tensions. The reduction is brought about by both central inspiratory and phasic pulmonary afferent mechanisms [19]. Similarly, it has been reported that tracheal intubation imposed during surgical procedures may provide some protection against activation of the TCR [20]. Babies under 6 months of age are excellent swimmers due to their DR: a baby's air passage blocks in contact to water as a consequence of the TCR, which explains the common observation of babies 'swimming' under water with open mouths [21].

Both reflexes, TCR and DR, have a well-known reciprocal influence on cardiac vagal and sympathetic activity in adults resulting in bradycardia that is unlike the conventional textbook description, initiated either by peripheral or central stimulation [8,10].

In fact, in some instances, HR may rebound to produce a delayed tachycardia. This is most probably indicative of a temporary difference in the activation of the autonomic outflows with the increase in cardiac sympathetic activity outlasting the vagal effect. Indeed, for DR, administration of methylscopolamine to inhibit vagal outflow may unmask tachycardia, which may then be abolished by subsequent β-adrenoceptor blockade with propranolol. In addition, vagally mediated bradycardia evoked by the stimulation of nasopharyngeal receptors was associated with simultaneous shortening of the electrocardiogram QT-interval, a measure of ventricular repolarization. Paton *et al.* have suggested that simultaneous parasympathetic and sympathetic coactivation may lead to a more efficient cardiac function. This coactivation pattern results in a greater cardiac output compared with the activation of the sympathetic limb alone, which is important when pumping blood into a constricted vascular tree such as in the case of DR and TCR [22].

Arterial blood pressure

Despite an increasing number of clinical reports on the TCR (for details see [23,24]), the physiological function of this brain stem reflex has not yet been fully explored. One important difference to the DR is that the typical response of the DR is characterized by arterial hypertension, whereas the 'classical' and central TCR leads to arterial hypotension. However, most of the measurements during breath-holding diving have only shown modest increases in MABP [24].

Cerebral blood flow

Another physiological similarity of both reflexes underlines the strong link between them: the DR results in an increase in cerebral blood flow (CBF), although there is some constriction of the cerebral resistance vessels [25]. For example, Joulia *et al.* demonstrated that, in control subjects during an apnea of 30 s, the CBF was increased by 60%, but for elite breath-hold divers and for the same apnea time, the CBF could be increased by 200% [24]. We have similar unpublished findings for TCR. However, it seems that many myogenic and neurogenic parameters may affect the TCR.

The autonomic nervous system

From a phylogenetic standpoint, the autonomic nervous system may be considered as a structure that has been progressively formed in the course of evolution in order to regulate energy, matter and information exchanges. The main function of the sympathico–adrenal system is to organize the function of the visceral organs for an action to be performed by the organism in response to the (unexpected) requirements of the environment ('fight or flight'). On the other hand, the role of the parasympathetic system is to prepare the visceral organs for an action to be performed by the organism on itself: self-protection (homeostasis), regeneration, recovery and reproduction. This system strongly underlies phylo- and ontogenetically determined patterns [26]. The fact that cardiac vagal activity is similar after stimulation of TCR and DR supports the hypothesis that the DR and TCR are closely linked. Whereas the goal of DR may be clear (saving the organism from drowning [oxygen-conserving effect] [27]), the purpose of the TCR has remained less obvious thus far.

Cardiac changes

Sensory loss as a result of skull-base tumors often goes unnoticed by the patient [28,29]. It may be found in only one of the modalities tested, as suggested by Nurmikko [30]. Loss of vibratory sense (128-Hz fork) is equated with loss of A-β fibers, loss of pinprick sensation is related to loss of A-δ fibers, and vasomotor and sudomotor abnormalities are seen in C-fiber dysfunction. The trigemino-depressor response followed by bradycardia is mediated by sympathetic inhibition and parasympathetic stimulation. The demonstration of these reflexes with low-level electrical stimulation further characterizes dysfunction, and may be a preoperative risk factor for the intraoperative occurrence of TCR. These changes in trigeminal structure of skull-base tumors may explain cardiac differences between the TCR and DR.

> "Paton *et al.* have suggested that simultaneous parasympathetic and sympathetic coactivation may lead to a more efficient cardiac function."

The relationship between bradycardia depth and tension shows that the occurrence of the TCR differs, explaining the wide range of TCR incidence in previous studies. It seems likely that the difference in incidence in previous data is mainly owing to differences in the analysis of measurement in HR technique, and the tension applied on the trigeminal nerve itself or structures innervated by it [2,5,15,18,31–35]. This is also apparent in our own experience. The afferent system is responsible for their differences, rather than the efferent system (including the vagus nuclei). Bradycardia occurs rapidly and recovers exponentially after the release of stimuli equally between TCR or DR.

Cardiac changes are always observed in association with bradycardia during the period of steady traction on the nerve itself or trigeminal innervated structures. HR monitoring during arrhythmia shows that the heart contracts soon after the preceding low-frequency contraction, and a supraventricular premature contraction occurs when the HR reaches approximately 60 beats/min [36]. Therefore, the arrhythmia may occur in order to compensate for bradycardia [36].

TCR, DR & phylogenesis

As a matter of fact, the oxygen-conserving TCR and its subsets seem to persist in humans [7,9,10,12,37,38]. In man, the DR may be considered as an archaic relic, which has functional importance only in phylogenetically lower ranked animals such as diver birds or amphibians. DR is indeed particularly developed in birds to inhibit cardiac and breathing activity during underwater feeding, necessary for individual and species survival (for example see [33]). In mammals, the DR is elicited by contact of the face with cold water and involves breath-holding, decreased ventilation, bradycardia, intense peripheral vasoconstriction and increased MABP, with the purpose being to prevent drowning and to provide an oxygen reservoir in the lungs, keeping the heart and brain adequately oxygenated at the expense of less hypoxia-sensitive organs [39].

In humans, washing the face or plunging it into cold water results in profound bradycardia and the redistribution of blood flow to the lungs, brain and heart, while radically reducing the blood flow to nonvital tissues [31]. However, the higher purpose of this reflex, especially the breath-hold response, in humans is equivocal [39], although it represents one of the most powerful autonomic reflexes. It has been observed that some newborns and infants with a developmental defect of the brain stem reflexogenic centers, interacting through the glossopharyngeal or trigeminal nerves and through the intervention of the ambiguous and the vagal dorsal nuclei, die of apnea and cessation of breathing [28–31].

The higher purpose of TCR in mammals – especially humans – is not fully understood at present. We think the following may be a very plausible explanation: the TCR may be important for breastfeeding during the first months of life. At that time, the newborn suckles for a relatively long period of time with its face against its mother. Consequently, the upper airways are partially obstructed by the mother's body, resulting in hypoventilation [21]. The DR, which is elicited by mechanical stimulation, results in bradycardia, hypotension and modifications in CBF in order to avoid damage to the developing brain. The role of the gastric hypermobility, another typical reaction elicited by stimulation of the TCR, also becomes evident in light of this. This also may explain the psychological or emotional dimension (the comfort due to hypotension/hyperventilation?) of these reflexes.

Some years ago, Schaller *et al.* hypothesized on the grounds of precise clinical and physiological observations that the term TCR subsumes the 'classical' central TCR, peripheral DR [40] and the oculocardiac reflex [41]. Grogaard and Sundell studied the 'trigemino diving reflex' in newborn lambs, reporting that this reflex was significantly reduced after treatment with β-adrenergic agonists [35].

> "…we propose that, from a physiological and even a phylogenetic standpoint, there is much evidence that the reflexes are closely linked."

As discussed previously, we propose that, from a physiological and even a phylogenetic standpoint, there is much evidence that the reflexes are closely linked. They are phylogenetically old reflexes especially useful for the underwater feeding of diver birds and amphibians. In humans, TCR and DR may be important during the breastfeeding period where the baby's upper airway is partially obstructed by close body contact with the mother. Their role in the pathogenesis of sudden infant death syndrome and for potential complications during neurosurgical procedures is also highly important. In fact, a better understanding of these reflexes will result in better patient care.

Conclusion

The links between DR and TCR are of great interest and widely accepted. DR is seemingly a peripheral subform of the TCR. However, thus far there are no convincing experimental and histopathological studies to prove these connections. Further studies are needed and will be especially interesting in case of sudden death after diving or trigeminal stimulation, as accurate examination of the brain stem on serial sections may reveal the morphological substrates responsible for these reflexes.

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