

Cardiac autonomic control in neurosurgery the example of trigemino-cardiac reflex

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Abstract

The trigemino-cardiac reflex (TCR) is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnoea or gastric hypermotility during stimulation of any of the sensory branches of the trigeminal nerve. In the present review, we summarize the knowledge about the TCR in relation to its two different ways of stimulation: (i) peripheral and (ii) central stimulation. We are the first to differentiate these two ways of occurrence of the TCR in our previous clinical work. From our studies, it seems that these differences are based on the varying autonomic control of the heart initiated either by peripheral or central stimulation. As despite the increasing clinical reports the physiological function of this brainstem reflex has not yet been fully explored, we give here new and important insights into this autonomic brainstem reflex. In addition, we try to give answers to the functional consequence of the different cardiac autonomic control of the TCR. By this physiological response, the adjustments of the systemic and cerebral circulations are initiated to divert blood to the brain or to increase blood flow within it. As a consequence, the striking age-related decline in the occurrence of the TCR seems to be the result of increased arterial stiffness. Our review gives therefore further insight into the potential brainstem circuit of the TCR, the most powerful autonomic reflex known in skull base surgery.

Key words: trigemino-cardiac reflex, autonomic control, heart rate, age, neurosurgery, skull base surgery.

Introduction

Autonomic control of the heart can be related to the Chinese yin and yang philosophy, such that the interrelation of opposites is crucial. The interaction between cardiac sympathetic and parasympathetic motor activity, which is classically characterized as opposite and reciprocal, can also be both synchronous and synergistic. One of the best examples of an autonomic reflex circuit is the trigemino-cardiac reflex (TCR), which was first described by Schaller et al. in 1999 [1] and represents the most powerful autonomic reflex that is known in adult humans. The TCR is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnoea or gastric hypermotility during stimulation of any of the sensory branches of the trigeminal nerve.

Autonomic co-activation develops during the occurrence of TCR [1-8], and of the diving reflex as well as from structures within the brain [9]. It is

suggested that the initial simultaneous co-activation may lead to a more efficient cardiac function giving greater cardiac output than activation of the sympathetic limb alone; this permits both a longer time for ventricular filling and a stronger contraction of the myocardium [10]. This may be important when pumping blood into a constricted vascular tree such as in the case during the diving response or – as first described by us – in peripheral stimulation of the TCR.

There is nothing known about the autonomic co-activation in the TCR, as there was nothing known regarding the differences in peripheral or central stimulation of the TCR until the present times. We are the first to describe the central [1] and – just recently – the peripheral stimulation of the TCR (submitted for publication). But, the peripheral stimulation of the TCR, even though it seems to be principally the same reflex pathway, sheds new light on the question of autonomic co-activation, knowledge of which we will summarize below.

Peripheral stimulation of the TCR

There is anatomical evidence that functionally different areas can be distinguished within the nasal mucosa, with regard to stimulation site and stimulus properties. Specifically, it has been shown in animals that mechanoreceptors are not equally sensitive throughout the nasal mucosa [11], with the most sensitive areas for mechanical stimuli in the posterior parts of the nose. In many animal species, including humans, pronounced respiratory and cardiovascular responses can be elicited by appropriate stimulation of the nasal mucosa in the awake state. These responses have been studied by many scientists in various animal models because they may be evoked by mechanical and electrical stimuli and by chemical irritants such as either vapour or tobacco smoke [12, 13]. Cardiac responses during nasopharyngeal stimulation (that evoke a diving-reflex-like response) are seen in a number of species [14]. In conscious rabbits, Nalivaiko et al. [15] reported that during the nasopharyngeal reflex, vagally-mediated bradycardia was associated with simultaneous shortening of the electrocardiogram QT interval. This QT shortening was prevented by propofol, and thus was sympathetically mediated. Blockade of reflex bradycardia by methylscopolamine unmasked a small tachycardia component. This latter response was suppressed by subsequent β -adrenergic blockade with propranolol.

The peripheral stimulation of the TCR is different from the central stimulation of the TCR, as the heart rate can rebound to produce a delayed tachycardia (data submitted for publication). This may be indicative of a temporal difference in the activation of the autonomic outflow with the increase in cardiac sympathetic activity outlasting the vagal effect. Thus, although the predominant vagal function is to

produce an immediate, potent bradycardia of several seconds duration, cardiac sympathetic activity appears to produce delayed positive chronotropic and underlying dromotropic actions, for example – as seen in our first description – a shortening of the electrocardiogram QT interval.

In addition to the diving response, the TCR can result in the development of an atrioventricular (AV) nodal rhythm or even asystole [1, 16] and ventricular ectopic beats; the latter supports the notion that there has to be some kind of sympathetic component, leading to increased outflow to the ventricles. Although infrequent, skull base surgery procedures can therefore induce a transient cardiac arrest that is vagally mediated [1]. Consistent with these findings is the observation that either mechanical or electrical stimulation of the cornea – including the oculocardiac reflex, a variant of the TCR – produced coactivation of the vagal and sympathetic outflows to the heart in the decerebrate rat [10]. This again could help account for the reported pathological cardiac events in patients with apparently healthy hearts.

Whether co-activation of the cardiac autonomic outflow by peripheral or central stimulation of the TCR generates a bradycardia or tachycardia presumably reflects the weighting of activity destined for the sino-atrial node in both autonomic neural limbs. It might be seen as a waste of metabolic energy. Berntson et al. suggested that coactivation provides precise control of both the response direction and magnitude, as well as fine tuning of target organ function [17]. Kollai et al. suggested that it maximized cardiac output through coordination of neural input to the ventricular muscle (sympathetic for contractility) and sino-atrial node (vagal for heart rate) [10]. In addition, bradycardia will reduce ventricular contractility via the Bowditch effect [18], so an increase in sympathetic outflow directed to the ventricular myocardium could prevent such a fall in contractility. This would be important for optimizing stroke volume and, hence, maintaining cardiac output and arterial pressure in the face of potent bradycardia.

Cardiac vagal endings contain several neuropeptides, including vasoactive intestinal peptide, neuropeptide Y, phenyl-histidine-isoleucine, substance P and enkephalins, which can be colocalized with acetylcholine. Vasoactive intestinal peptide and phenyl-histidine-isoleucine have the same effect as noradrenaline in increasing heart rate and could explain the observation that activation of somatic nociceptors evoked an atropine-sensitive tachycardia. Thus, it may be that in some instances vago-sympathetic coactivation results in a true synergistic effect on heart rate. Alternatively, the release of these peptides may act to modulate the efficacy of noradrenaline release from cardiac sympathetic terminals and could explain the non-linear interaction between autonomic outflows described by Levy [19].

Central stimulation of the TCR

As described earlier by one of the authors [1], central stimulation of the TCR produces a clear-cut inhibition of the inferior cardiac sympathetic nerve and profound activation of the cardiac vagal branch activity. This mechanism is different from that discussed above for peripheral stimulation of the TCR, but is earlier described by us in detail [1, 9]. Here, the afferent pathway continues along the short internuncial nerve fibres in the reticular formation to connect with the efferent pathway in the motor nucleus of the vagus nerve. In our previous experience, the autonomic co-activation seems not to play a role in the central stimulation of the TCR.

Suggested cerebral changes by the TCR

The TCR is, in our opinion, a specific example of a group of related responses generically defined by Wolf as oxygen-conserving reflexes [20]. Within seconds after reflex initiation, there is a powerful and differentiated activation of sympathetic nerves. The suggested effect of the TCR in the brain is consecutive elevation in cerebral blood flow (CBF) that is not associated with changes in cerebral metabolic rate for oxygen (CMRO₂) or cerebral glucose metabolic rate (CMRglc) and hence represents a primary cerebrovascular vasodilatation. The brain can protect itself from ischaemia by distinct (endogenous) physiological mechanisms, which probably involve two separate systems of neurons in the CNS [7, 21]. The one which mediates a reflexive neurogenic neuroprotection emanates from oxygen-sensitive sympathoexcitatory reticulospinal neurons of the rostral ventrolateral medulla (RVLM). These cells, excited within seconds by reduction in blood flow or oxygen, initiate the systemic vascular components of the oxygen-conserving diving reflex [22]. They profoundly increase rCBF without changing CMRO₂ and CMRglc and, hence, rapidly and efficiently provide the brain with oxygen. Upon cessation of the stimulus the systemic and cerebrovascular adjustments return to normal [23]. The system mediating reflex protection projects via as-yet-undefined projections from the RVLM to the upper brainstem and/or thalamus to engage a small population of neurons in the cortex which appear to be dedicated to transducing a neuronal signal into vasodilation.

Two lines of evidence indicate that the RVLM neurons are essential for the expression of the cerebrovascular vasodilation elicited by hypoxia. First, electrical stimulation of RVLM in intact or spinalized rats site-specifically and dose-dependently elevates rCBF, but not CMRO₂ or CMRglc [24]. In this manner these data replicate hypoxic vasodilatation [25]. The response can only be attributed to stimulation of the reticulospinal sympathoexcitatory neurons since these are the only neurons in the region excited by

over 50% elevation of CBF produced by hypoxaemia. The fact that such lesions do not affect the vasodilatation elicited by hypercarbia indicates that the response is stimulus selective [25]. Thus, much of the cerebrovascular vasodilatation elicited in the cerebral cortex by hypoxaemia is a reflex which results from excitation of oxygen-sensitive brainstem neurons, and not by a direct effect of hypoxia on blood vessels [26] nor by stimulation of arterial chemoreceptors whose activity, while regulating blood flow to most vascular beds, is without effect on the cerebral circulation [27]. It also appears to relay the central neurogenic vasodilatation elicited from other brain regions, including excitation of axons innervating the fastigial nucleus. This mode of protection would be initiated under conditions of global ischaemia and/or hypoxaemia because the signal is detected by medullary neurons.

That the brain may have neuronal systems dedicated to protecting itself from (ischaemic) damage, at first appearing to be a novel concept, is, upon reflection, not surprising since the brain is not injured in naturalistic behaviours characterized by very low levels of rCBF, such as diving or hibernation [28, 29]. Such neuroprotective adaptations may also underlie preconditioning strategies [29]. The diving reflex, hibernation and ischaemic tolerance appear to involve at least partially similar physiological mechanisms because most of the signals, transducers and effectors that are well-established in ischaemic tolerance have also been demonstrated in hypoxia-tolerant or hibernating animals [30]. A better and more detailed understanding of the pathways, transmitters and molecules engaged in such protection may provide new insights into novel therapies for a range of disorders characterized by neuronal death [29]. Recent clinical studies suggest such an endogenous neuroprotective effect in the human brain [29].

Functional significance of autonomic control

Unlike the conventional textbook picture of reciprocal control of cardiac vagal and sympathetic nervous activity, as seen for example during baroreceptor reflex stimulation, many other reflexes – for example the TCR – involve simultaneous co-activation of both autonomic limbs. Indeed, even at “rest”, the heart receives tonic drives from both sympathetic and parasympathetic cardiac nerves. It is suggested that simultaneous co-activation may lead to more efficient cardiac function, giving greater cardiac output than activation of the sympathetic limb alone; this permits both a longer time for ventricular filling and a stronger contraction of the myocardium.

Simultaneous co-activation allows precise control of the response direction, which is determined by the dominating limb of the autonomic nerve, and hence allows the fine tuning of target organ function.

Since the dynamic range and the gain of the response is restricted in this situation, the tendency here is towards stabilization of the functional state of the target organ. Kollai and Koizumi [10] made a suggestion that the functional significance of vago-sympathetic co-activation may be to coordinate the relationship between ventricular contractility and heart rate so as to maximize cardiac output. They found that during simultaneous cardiac vago-sympathetic co-activation, vagal activity is mainly responsible for chronotropic effects, and suggested that the “concomitant increase in sympathetic outflow targets the ventricular myocardium” [10]. In an attempt to prove this interpretation, in a follow-up paper, these authors demonstrated that direct simultaneous electrical stimulation of vagal and sympathetic cardiac nerves (using spike trains to mimic endogenous activity) resulted in a greater increase in cardiac output than did sympathetic stimulation alone [31].

In the TCR, the elicited bradycardia may represent an adaptive physiological reaction that protects the heart from hypoxia by dramatically reducing oxygen consumption (the heart is an organ with a major demand for oxygen due to both its inherently high metabolic rate and inability to respire anaerobically). Since bradycardia causes a substantial fall in ventricular contractility via a non-neural mechanism (Bowditch effect) [18], it may be that the increase in sympathetic outflow to the ventricular myocardium serves the purpose of counteracting the rate-dependent fall in contractility, thereby optimizing stroke volume. But neither cardiac autonomic nervous system indices nor (low) ejection fraction allows us to identify the patients before skull base surgery who will develop TCR.

Influence of age on autonomic function

As a substantial part of our skull base surgery patients are of higher age, the question whether age may have some influence on autonomic function is of special interest in relation to the TCR. Physiological aging effects of cardiovascular circulation are mainly caused by alterations of the autonomic nervous system, adrenoceptors' responsiveness [32], and other neurohumoral systems, for example the renin-angiotensin-aldosterone axis [33]. Studies in healthy men showed that baroreflex buffering is reduced with age [34], and this decrease is related to an increase in basal muscle sympathetic nerve activity and reduction of the 1-adrenergic vascular responsiveness [35]. Assessment of heart rate variability by spectral analysis in relation to sex showed that men and postmenopausal women have higher low-frequency R-R intervals (LF_{RRi}), lower high-frequency R-R intervals (HF_{RRi}), and an increased LF to HF ratio [36]. The dramatic and consistent patterns of neuropathy that characterize the aging autonomic nervous system of

the heart are candidate mechanisms for some of the age-related declines in function evidenced in the elderly.

One may suggest that TCR may be influenced by aging-related changes in both afferent cardiac and pulmonary reflex arch, which do not necessarily reflect age-related changes in efferent vagal activity. In contrast, the cold face test does not involve apnoea, forced breathing or any other changes in ventilatory pattern other than resting tidal airflow, and has been shown previously to be well tolerated in old people [37].

The question of efferent cardiac vagal activity in old age has been studied previously, principally by Kaijser and Sachs [38] and by Ingall et al. [39]. Both of these groups reported age-related decreases in cardiac vagal activity in response to a variety of autonomic function tests, including the Valsalva manoeuvre, sinus arrhythmia, expiratory/inspiratory ratio and apnoeic facial immersion (diving reflex). However, each of these tests may be influenced by aging-related changes in both respiratory function and afferent cardiopulmonary reflexes, which do not necessarily reflect age-related changes in efferent cardiac vagal activity. In contrast, the cold face test does not involve apnoea, forced breathing or any other changes in ventilatory pattern other than resting tidal air flow, and has been shown previously to be well tolerated in old people [37]. Collins et al. [40] have described significantly less bradycardia in healthy elderly subjects compared with healthy young subjects in response to facial cooling with cold air jets, which contrasts with the lack of a statistically significant difference between the young and elderly groups in the present study. On the basis of our findings, the occurrence of the TCR cannot be attributed to effects of aging on efferent cardiac vagal or vascular sympathetic pathways. This indicates that the age-related loss of sensitivity of autonomic activation may result from changes in: (i) afferent TCReflex fibres, or (ii) central brainstem TCReflex gain. It is implausible that there is selective, age-related, afferent TCReflex autonomic dysfunction in the presence of normal efferent parasympathetic and sympathetic function, making (i) an unlikely possibility. At the present time, there is no non-invasive experimental means of measuring TCR afferent or central gain function in humans. However, two well observed phenomena associated with aging and arteriosclerosis, i.e. increased resting muscle nerve sympathetic activity, provide circumstantial evidence that the age-related decrease in the occurrence of TCR results primarily from loss of arterial compliance.

Several studies have shown that aging is associated with significantly increased muscle nerve sympathetic activity at rest [41, 42]. Yamada et al. [42] have suggested that this phenomenon, like carotid sinus hypersensitivity, also results from reduced arterial

wall compliance. The consequent gradual decrease in afferent TCR neural activity leads to gradually increased efferent TCR sympathetic outflow, manifested as increased muscle nerve sympathetic activity at rest. This hypothesis is made more plausible by the fact that TCR sensibility is markedly reduced with advancing age [43].

The mechanism of the age-related decrease in the occurrence of the TCR, if there exists such a phenomenon and it is not only a bias, remains therefore speculative. However, our data and the literature give good evidence that the age-related decrease in the occurrence of the TCR is not attributable to impairments in the efferent sympathetic or parasympathetic system components of the TCR pathway.

In conclusions taken together, our observations on the peripheral or central stimulation of the TCR thus indicate that patients with a less favourable outcome of skull base surgery a priori have altered sympathetic as well as parasympathetic cardiac control leading to the occurrence of a TCR. The autonomic co-activation after peripheral stimulation may open new windows in the treatment of ischaemic lesions, insofar as one may speculate on initiation of some kind of "ischaemic tolerance" by this way.

Our review shows that the decrease in the occurrence of the TCR in healthy elderly people is not associated with reduced brainstem efferent vagally or sympathetically mediated cardiovascular responses to physical and cognitive stresses. Since a selective afferent TCR neural defect is unlikely, and since aging is associated with increased central brainstem TCR gain, we believe that the present data support the theory that the age-related decline in the occurrence of the TCR is the result of increased arterial stiffness.

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