Expert Review of Cardiovascular Therapy

ISSN: 1477-9072 (Print) 1744-8344 (Online) Journal homepage: informahealthcare.com/journals/ierk20

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To cite this article: Tumul Chowdhury, Nora Sandu, Pooyan Sadr-Eshkevari, Cyrill Meuwly & Bernhard Schaller (2014) Trigeminocardiac reflex: current trends, Expert Review of Cardiovascular Therapy, 12:1, 9-11, DOI: 10.1586/14779072.2014.862498

To link to this article: https://doi.org/10.1586/14779072.2014.862498

Published online: 22 Nov 2013.

Trigeminocardiac reflex: current trends

Expert Rev. Cardiovasc. Ther. 12(1), 9–11 (2014)

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Since the first introduction of the trigeminocardiac reflex (TCR) in 1999, substantial new knowledge about this brainstem reflex has been created. First, by different clinical case reports and case studies, and second, from basic research that gives inputs from bench to bedside. In the present work, the authors therefore introduce the molecular/anatomical knowledge of the TCR and show its different connections to clinical aspects. Special reference is given to prevention and treatment of the TCR; but always with a link to knowledge of the basis sciences. In such a context different topics of future interest are introduced.

Trigeminocardiac reflex (TCR) is a well-established neurogenic reflex and in the past 20 years, there has been developed a tremendous interest among neuroscientists and clinicians to explore this reflex in toto. Though considered as one of the important brainstem reflexes, its exact mechanism and clinical significance are still not clear. TCR has been investigated in many neurosurgical procedures including skull base surgery, neurointerventional procedures and neurovascular surgery [1–13]. The usual manifestation of TCR includes bradycardia, asystole, hypotension, apnea and gastric hypermotility. This reflex mainly represents an afferent limb that relay sensation through trigeminal nerve and manifest its effects via vagus nerve that comprises its efferent limb. The various nuclei described in TCR pathway are the trigeminal nucleus caudalis, parabrachial nucleus, the rostral ventrolateral medulla oblongata, the dorsal medullary reticular field and the paratrigeminal nucleus [1]. There is complex interaction among these nuclei, and there is suppression or activation of signals from one or more nuclei that regulates the activation of TCR and probably also determine the manifestations of this reflex [1,14]. In addition, some of the interactions of different receptors and their affinity to different biomolecules have been investigated to elucidate the mechanism of TCR; however, it is still inconclusive. In the future, there should be a better understanding of these molecular operations to better understand the different potential links of this phylogenetic reflex [14,15].

TCR has been reported with different manifestations throughout the literature; therefore, now it is plausible that TCR has different subtypes that include peripheral TCR (peripheral divisions to ganglion), central TCR (ganglion to nucleus) and Ganglion Gasseri-related TCR. In addition, peripheral TCR can be further divided into oculocardiac reflex and maxilomandibular cardiac reflex [5,13]. According to the literature, peripheral TCR may or may not be associated with hypotension, whereas central TCR has usually been reported to be associated with hypotension [3].

The coactivation of parasympathetic (activation) limb and sympathetic outflow (inhibition) during central TCR may produce significant depressor response (a depressor response significantly more profound than that of peripherally triggered) [1]. Recently published report has demonstrated these different types of TCR occurring in the same patient. On the other hand, Diving reflex, which has long been regarded as the most powerful autonomic reflex, presents with sudden vasoconstriction followed by apnea and bradycardia. This picture closely resembles that of and hence may be considered as a modified peripheral TCR [3]. Ganglion Gasseri

Keywords: asystole • case report • central • chronic • oxygen-conserving reflex • peripheral • skull base surgery • trigeminocardiac reflex

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 10.1586/14779072.2014.862498 ISSN 1477-9072

stimulation has shown variable clinical manifestation [6]. Up to now, several researchers have also tried to explore the biochemical significance of the reflex [3,14,16]. It has been highlighted that TCR, when incited, produces intense cerebrovasodilation with no accompanied rise in oxygen consumption and therefore should be regarded as an oxygen-conserving reflex [15]. TCR is found to play a physiological role as an oxygen-conserving reflex through which the adjustments of the systemic and cerebral circulations are initiated to divert blood to the brain or to increase blood flow within it. On the other hand, TCR may produce catastrophic consequences if not promptly recognized and treated [1]. Therefore, a better molecular understanding of this reflex in the near future supports the hope to have better knowledge about its risk factors and treatment options.

Among several important facts about TCR, its relation with postoperative outcome has also been investigated in few surgeries and interestingly, episodes of TCR have been associated with compromised functional outcomes in vestibular schwannoma resection surgeries. This is an interesting finding that could provide some explanation about the clinical significance of this unique reflex. Other studies are being carried out to find out its occurrence in other neurosurgical procedures and the corresponding outcomes. Furthermore, TCR episodes have been reported in non-neurosurgical procedures including maxillofacial surgeries, nasal surgeries, nasal endoscopic procedures, dental extractions and injections, and even during local infiltration [3,17–19]. Similarly, strength of stimulus, which is considered as most important inciting factor is also challenged in some recent papers [1–3]. Even mild skin traction has been shown to incite TCR and can produce catastrophic consequences if not monitored vigilantly. In addition, various risk factors including higher vagotonicity, light plane of anesthesia, use of different drugs (opioids, b-blockers, calcium channel blocker), dural stimulation (traction, chemical, electrical) and other physiological conditions (hypoxia, hypercapnia, acidosis) have been linked with the occurrence of TCR. Recent experiments suggested that nicotine exposure may be a risk factor inciting TCR and further explained the association of nicotine exposure with sudden infant death syndrome (SIDS) [3]. A further step in the TCR research would be to categorize these risk factors according to their consecutive molecular reaction. But here is still a gap between bench and bedside [20].

As mentioned before, the importance of TCR is not merely intraoperative; few reports have highlighted a chronic subtype of TCR. Researchers have further described that TCR can persist for few days to several months in traumatic patients and can repeatedly incite hemodynamic perturbations that may present as diagnostic dilemma. This finding would certainly give new insight in the management of the patients with orbital/zygomatic/maxillofacial fractures who present with cardiovascular changes that are not related to true cardiac events [1–3]. Similarly, some of the other mechanisms including bruxism and SIDS have been linked with episodes of TCR. Bruxism, rhythmic masticatory muscle activity, involves multiple occurrences of tachycardia episodes due to micro arousals during sleep. However, rhythmic masticatory muscle activity triggers TCR and stabilizes the heart rate. Therefore, TCR seems to be a protective mechanism during sleep. On the other hand, exaggeration of peripheral TCR (diving reflex) has been associated with SIDS. The over activity of histamine receptors and nicotine exposure both may exaggerate TCR and further explain the association of TCR with SIDS [3]. These findings would definitely provide new pathways for the proper understanding and management of SIDS and opens the gate for further researches.

In conclusion, TCR has been emerged as one of the most important phenomena in neuroscience. The role of various anatomical locations, different tumor pathologies, type of anesthetic (volatile vs total intravenous anesthetics) are some of the areas that are yet to be explored in context to TCR [20]. TCR might be a principal phenomenon in some neurological conditions including stroke, seizures, sleep bruxism, etc. that need to be further explored. The future role of TCR underlies in exploring its exact mechanism, neuroprotective role, different subtypes, effects on functional outcome and association of TCR with other neurological conditions. At the current stage, further molecular knowledge is needed to better understand this clinically challenging reflex.

Financial & competing interest disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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