THE TRIGEMINO-CARDIAC REFLEX: BEYOND THE DIVING REFLEX

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THE TRIGEMINO-CARDIAC REFLEX: BEYOND THE DIVING REFLEX

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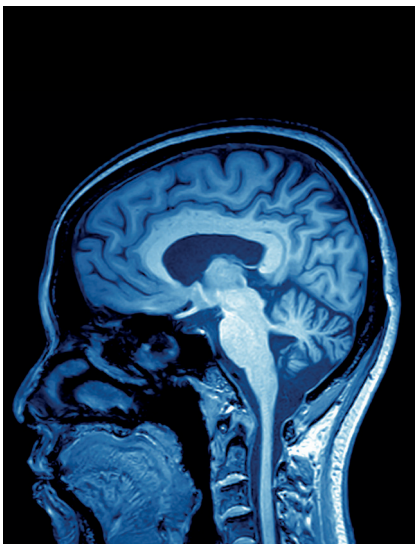

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The trigemino-cardiac reflex (TCR) is a well established brain-stem reflex and commonly manifests as bradycardia, asystole, hypotension and / or apnea. This phenomenon was extensively explored in the recent past. However, the area related to its exact bio-physiological mechanism, neuro-anatomical linkages, clinical implications, its role in non neurological events and future directions should need to be further investigated. Therefore, this present research topic on TCR would mainly focus on various aspects of TCR and present a comprehensive and exhaustive overview about a phenomena that gains more and more interest during the last few years. Our goal is to present models about the different aspects of the TCR to develop in-depth understanding of TCR.

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EDITORIAL
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Editorial: The Trigeminocardiac Reflex: Beyond the Diving Reflex

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Keywords: trigeminocardiac reflex, models, theoretical, skull base surgery, neuroanesthesiology, neuroanatomy

Editorial on the Research Topic

The Trigeminocardiac Reflex: Beyond the Diving Reflex

The trigeminocardiac reflex (TCR) is a well-described and also well-known brainstem reflex that is extensively researched and reported in clinical neurosciences during the last nearly 20 years (Schaller et al., 1999). During this time period, investigators have explored the physiological and/or pathological, but also the neurobiological nature of this unique reflex (Schaller, 2004; Filis et al., 2008; Schaller et al., 2008a, 2009b; Arasho et al., 2009; Meuwly et al., 2013; Lemaitre et al., 2015) as well as its consequences on various surgical outcomes (Gharabaghi et al., 2006; Schaller et al., 2007, 2008b). In addition, albeit few animal experiments on the TCR models also provided its relationship with cerebral hemodynamics and metabolism (Sandu et al., 2010; Lapi et al.; Buchholz et al.) and included the concept of oxygen conserving reflex into the TCR (Schaller et al., 2009a). Currently, we are in a new phase of the TCR research: We have to understand in which kind of diseases the TCR might also play a role and how we could utilize this information for developing future interventions and treatment modalities (see for example, Cornelius et al., 2010). It is therefore the time to reflect what we have achieved in the TCR research so far.

From the very beginning, the TCR was considered as the most powerful autonomous reflex in humans and mammals. For a substantial time-span, the principal knowledge of the TCR was especially and nearly exclusively related to a fundamental work written in 1999 that introduced this reflex into various neurosurgical procedures, especially of the skull base (Schaller et al., 1999). The scientific evidence of the reflex's validity/reliability was provided on a causal relationship basis, and the TCR arc was described based on the trigeminal and cardioinhibitory vagus nerves as the afferent and efferent pathways respectively (Schaller et al., 1999). This initial case series introduced, for the first time, an emergent TCR definition based on clinical, but also theoretical consideration. Thereafter, the in the following years published case reports could focus mainly on the differentiation between the peripheral and the central stimulation (Schaller et al., 2009b) providing strong evidence that the peripheral triggered TCR (via the spinal nucleus of the trigeminal nerve to the Kölliger-Fuse nucleus) is different from the TCR triggered by central stimulation (via the nucleus of the solitary tract to the lateral parabrachial nucleus) or any trigeminal stimulation in other locations (Chowdhury et al., 2014c). Also, interesting in this context is the development of the spinal cardiac reflex (Chowdhury and Schaller, 2017). Only recently, there could be found a more detail definition model of the TCR that included all these new findings (Meuwly et al., 2015b; Meuwly et al.).

In-addition, it was also investigated whether other skull base operations (excluding vestibular schwannomas) were accompanied by an intraoperative TCR occurrence: trans-sphenoidal surgery (Schaller, 2005a) and during Janetta operations (Schaller, 2005b) could be identified as further interventions aligned with a TCR. In these times, the issue of generalization of this already existing fragmented TCR knowledge has appeared in the (scientific) medical literature with

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regularity. Further research for TCR in different skull base approaches were forced to facilitate this generalization (Spiriev et al., 2011a,b) also pointing out the eminent importance of the TCR on the functional outcome after skull base surgery. Focusing on hearing and tinnitus function in patients with vestibular schwannoma has demonstrated the intraoperative hypotension owing to the TCR occurrence to be a negative prognostic factor for hearing preservation and postoperative tinnitus (Schaller et al., 2008b). Similarly, few reports also investigated various generally-based predisposing factors for TCR occurrences (Chowdhury et al., 2014a,b). These factors include hypercapnia, hypoxemia, light anesthesia, high resting vagal tone in children, narcotics such a sufentanil and alfentanil, preoperative β-blockers and calcium channel blockers (Meuwly et al., 2015a).

In a further stage of the TCR research, few surrogate models were developed to describe the better knowledge and understanding about the TCR behavior (Meuwly et al., 2015a,b, 2016; Meuwly et al.). These are not only useful to define and classify the TCR in a precise manner, but these also present the standardized definition of the TCR for the clinical research purposes. At this stage, the TCR phenomenon was also linked with various other problems including sudden infant death syndrome, sleep disorders (obstructive sleep apnea) and other neurological disorders (Chowdhury and Schaller; Golanov et al.; Singh et al.; Chowdhury and Schaller; Chowdhury et al.). This information opened the gate for further research of the TCR that was mainly highlighted during the intraoperative period.

Importantly, now it is known that the TCR physiology is not limited to surgical domain, its clinical implications are quite wide and variable. These manifestations can be from trivial to fatal as well as acute, sub-acute and even, chronic. In-addition, classical symptoms may not be present especially in chronic form of the TCR and make diagnosis even more challenging.

Therefore, the present research topic "The trigeminocardiac reflex: Beyond the diving reflex" imparts a new understanding of the TCR phenomenon and opens the gate for further research on this unique reflex for better understanding various neurological conditions and hopefully, would also assist in developing some treatment/interventions treat such conditions.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

Arasho, B., Sandu, N., Spiriev, T., Prabhakar, H., and Schaller, B. (2009). Management of the trigeminocardiac reflex: facts and own experience. *Neurol. India* 57:375. doi: 10.4103/0028-3886.55577

Chowdhury, T., Cappellani, R., and Schaller, B. (2014a). Chronic trigemino-cardiac reflex in patient with orbital floor fracture: role of surgery and first description. *J. Neurosurg. Anesthesiol.* 26:91. doi: 10.1097/ANA.0b013e3182a1a691

Chowdhury, T., Cappellani, R. B., and Schaller, B. (2014b). Retrogasserian glycerol rhizolysis: first description of occurrence trigeminocardiac reflex. *J. Neurosurg. Anesthesiol.* 26, 86–87. doi: 10.1097/ANA.0b013e318297f96a

Chowdhury, T., Sandu, N., Meuwly, C., Cappellani, R. B., and Schaller, B. (2014c). Trigeminocardiac reflex: differential behavior and risk factors in the course of the trigeminal nerve. *Future Neurol.* 9, 41–47. doi: 10.2217/fnl.13.62

Chowdhury, T., and Schaller, B. (2017). The negative chronotropic effect during lumbar spine surgery: a systemic review and aggregation of an emerging model of spinal cardiac reflex. *Medicine* 96:e5436. doi: 10.1097/MD.0000000000005436

Cornelius, J. F., Sadr-Eshkevari, P., Arasho, B. D., Sandu, N., Spiriev, T., Lemaitre, F., et al. (2010). The trigemino-cardiac reflex in adults: own experience. *Expert Rev. Cardiovasc. Ther.* 8, 895–898. doi: 10.1586/erc.10.74

Filis, A., Schaller, B., and Buchfelder, M. (2008). Trigeminocardiac reflex in pituitary surgery. A prospective pilot study. *Der Nervenarzt* 79, 669–675. doi: 10.1007/s00115-007-2380-3

Gharabaghi, A., Koerbel, A., Samii, A., Kaminsky, J., von Goesseln, H., Tatagiba, M., et al. (2006). The impact of hypotension due to the trigeminocardiac reflex on auditory function in vestibular schwannoma surgery. *J. Neurosurg.* 104, 369–375. doi: 10.3171/jns.2006.104.3.369

Lemaitre, F., Chowdhury, T., and Schaller, B. (2015). The trigeminocardiac reflex – a comparison with the diving reflex in humans. *Arch. Med. Sci.* 11, 419–426. doi: 10.5114/aoms.2015.50974

Meuwly, C., Chowdhury, T., Sandu, N., Reck, M., Erne, P., and Schaller, B. (2015a). Anesthetic influence on occurrence and treatment of the trigemino-cardiac reflex: a systematic literature review. *Medicine* 94:e807. doi: 10.1097/MD.0000000000000807

Meuwly, C., Chowdhury, T., Sandu, N., and Schaller, B. J. (2016). Meta-areas of the trigeminocardiac reflex within the skull base: A neuroanatomic "thinking" model. *J. Neurosurg. Anesthesiol.* 28, 437–438. doi: 10.1097/ANA.0000000000000240

Meuwly, C., Chowdhury, T., and Schaller, B. (2013). Topical lidocaine to suppress trigemino-cardiac reflex. *Br. J. Anaesth.* 111, 302–302. doi: 10.1093/bja/aet244

Meuwly, C., Golanov, E., Chowdhury, T., Erne, P., and Schaller, B. (2015b). Trigeminal cardiac reflex: new thinking model about the definition based on a literature review. *Medicine* 94:e484. doi: 10.1097/MD.0000000000000484

Sandu, N., Spiriev, T., Lemaitre, F., Filis, A., and Schaller, B. (2010). New molecular knowledge towards the trigemino-cardiac reflex as a cerebral oxygen-conserving reflex. *ScientificWorldJournal.* 10, 811–817. doi: 10.1100/tsw.2010.71

Schaller, B. (2005a). Trigemino-cardiac reflex during transsphenoidal surgery for pituitary adenomas. *Clin. Neurol. Neurosurg.* 107, 468–474. doi: 10.1016/j.clineuro.2004.12.004

Schaller, B. (2005b). Trigemino-cardiac reflex during microvascular trigeminal decompression in cases of trigeminal neuralgia. *J. Neurosurg. Anesthesiol.* 17, 45–48.

Schaller, B., Cornelius, J. F., Prabhakar, H., Koerbel, A., Gnanalingham, K., Sandu, N., et al. (2009a). The trigemino-cardiac reflex: an update of the current knowledge. *J. Neurosurg. Anesthesiol.* 21, 187–195. doi: 10.1097/ANA.0b013e3181a2bf22

Schaller, B., Cornelius, J. F., Sandu, N., Ottaviani, G., and Perez-Pinzon, M. A. (2009b). Oxygen-conserving reflexes of the brain: the current molecular knowledge. *J. Cell. Mol. Med.* 13, 644–647. doi: 10.1111/j.1582-4934.2009.00659.x

Schaller, B. J. (2004). Trigeminocardiac reflex. *J. Neurol.* 251, 658–665. doi: 10.1007/s00415-004-0458-4

Schaller, B. J., Filis, A., and Buchfelder, M. (2007). Detection and prevention of the trigeminocardiac reflex during skull base surgery. *Acta Neurochir.* 149:331. doi: 10.1007/s00701-006-1088-7

Schaller, B. J., Filis, A., and Buchfelder, M. (2008a). Trigemino-cardiac reflex in humans initiated by peripheral stimulation during neurosurgical skull-base operations. Its first description. *Acta Neurochirurgica* 150:715. doi: 10.1007/s00701-008-1602-1

Schaller, B. J., Rasper, J., Filis, A., and Buchfelder, M. (2008b). Difference in functional outcome of ipsilateral tinnitus after intraoperative occurrence of the trigemino-cardiac reflex in surgery for vestibular schwannomas. *Acta Neurochir.* 150, 157–156. doi: 10.1007/s00701-007-1476-7

Schaller, B., Probst, R., Strebel, S., and Gratzl, O. (1999). Trigeminocardiac reflex during surgery in the cerebellopontine angle. *J. Neurosurg.* 90, 215–220. doi: 10.3171/jns.1999.90.2.0215

Spiriev, T., Kondoff, S., and Schaller, B. (2011a). Trigemino-Cardiac-Reflex-Examination-Group. Cardiovascular changes after subarachnoid hemorrhage initiated by the trigeminocardiac reflex – first description of a case series. *J. Neurosurg. Anesthesiol.* 23, 379–380. doi: 10.1097/ANA.0b013e3182312486

Spiriev, T., Kondoff, S., and Schaller, B. (2011b). Trigeminocardiac reflex during temporary clipping in aneurismal surgery: first description. *J. Neurosurg. Anesthesiol.* 23, 271–272. doi: 10.1097/ANA.0b013e3182204c2c

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MINI REVIEW
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Sleep Disorders: Is the Trigemino-Cardiac Reflex a Missing Link?

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Trigeminal innervated areas in face, nasolacrimal, and nasal mucosa can produce a wide array of cardiorespiratory manifestations that include apnea, bradypnea, bradycardia, hypotension, and arrhythmias. This reflex is a well-known entity called "trigemino-cardiac reflex" (TCR). The role of TCR is investigated in various pathophysiological conditions especially in neurosurgical, but also skull base surgery procedures. Additionally, its significance in various sleep-related disorders has also been highlighted recently. Though, the role of diving reflex, a subtype of TCR, has been extensively investigated in sudden infant death syndrome. The data related to other sleep disorders including obstructive sleep apnea, bruxism is very limited and thus, this mini review aims to investigate the possible role and correlation of TCR in causing such sleep abnormalities.

Keywords: trigemino-cardiac reflex, sleep apnea, bruxism, bradycardia, diving reflex

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INTRODUCTION

Sleep disorders are a common increasing health problem in today's industrialized world and can have a significant impact on quality of life and of working. They commonly manifest as excessive daytime sleepiness, difficulty initiating or maintaining sleep, or abnormal movements, behaviors, and sensations occurring during sleep. Sleep bruxism, thought to be a more intense form of rhythmic masticatory muscle activity (RMMA), has a prevalence of about 8% (1). Sleep apnea syndrome affects up to 3–5% of the adult human population. Unfortunately, the majority of sleep disorders remain undiagnosed to a large extent. Young et al. in 1997 reported that 80–90% of adults with clinically significant sleep-disordered breathing remain undiagnosed (2).

In this regard, the role of the trigemino-cardiac reflex (TCR) is never extensively explored. The TCR is one of the most powerful autonomic reflexes of the body that helps reduce heart rate under challenging situations by acting as oxygen-conserving reflex (3–5). The trigeminal nerve can be stimulated anywhere along its course and causes sympathetic withdrawal and parasympathetic over activity through the vagus nerve resulting in bradycardia or even asystole, apnea, bradypnea, and hypotension. Various manifestations of the TCR include the naso-cardiac reflex, peripheral TCR, the diving reflex (DR), and the central TCR (6–10). Interestingly, DR, a subtype of TCR, has been hypothesized to have a role in sudden infant death syndrome (SIDS) (11) and the TCR is also linked to sleep disorders like sleep-related bruxism (SB) (12). It is reported that sudden microarousals (MA) occurring in the brain due to airway obstruction during sleep cause tachycardia, which stimulates RMMA and teeth grinding that activate the TCR resulting in bradycardia. The physiological basis and importance of conditions like sleep bruxism and obstructive sleep apnea (OSA) are still not completely understood. This is a narrative mini review and aims to provide facts and hypotheses that the TCR plays a central role in various sleep disorders.

NORMAL SLEEP

About one-third of our lives are spent sleeping. Two types of sleep have been described: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM further has four stages, 1, 2, 3 and 4, representing a continuum of relative depth of sleep. NREM and REM cycle throughout the night. Normal individuals first enter sleep in NREM, which progresses through stages 1, 2, 3 and 4, and then enter REM sleep. NREM sleep occupies 75–80% of sleep and REM sleep accounts for 20–25%. The average length of NREM–REM cycles is 70–100 min initially and later increases to 90–120 min as sleep progresses (13). The duration of REM sleep in each cycle increases as the night progresses.

The four stages of NREM sleep have characteristic brain physiology. Stage 1 accounts for 2–5% of total sleep and gets easily disrupted by loud noise. EEG waves in this stage show transition from alpha waves to low voltage, mixed frequency waves. Stage 2 accounts for 45–55% of total sleep and is characterized by low voltage, mixed frequency waves with sleep spindles and K-complexes. Stages 3 and 4, together called slow-wave sleep, are characterized by high voltage, slow wave activity. Stage 3 accounts for 3–8% and stage 4 for 10–15% of total sleep. Among all stages of NREM sleep, arousal threshold is highest for stage 4 (13). REM sleep is characterized by theta waves and slow alpha waves, muscle atonia, and bursts of REMs (13). Most of dreaming and memory consolidation occur during REM sleep (14).

Non-rapid eye movement and REM sleep vary considerably concerning physiological changes (15, 16). Broadly, brain activity, heart rate, blood pressure, cerebral blood flow, and respiration decrease during NREM and increase in REM sleep. Muscle tone is absent, and body temperature regulation is disturbed during REM sleep and sexual arousals occur more frequently in REM sleep. Airway resistance increases during both NREM and REM sleep, compared to wakefulness (17).

SLEEP DISORDERS

Around 90 different sleep disorders have been identified so far. The third edition of International Classification of Sleep Disorders (ICSD-3) classifies sleep disorders into seven major diagnostic sections—insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders (18). The ICSD-3 classifies OSA as a sleep-related breathing disorder while SB is classified as a sleep-related movement disorder. OSA, usually occurs due to mild to severe collapse of the airway (mainly obstruction by soft tissues) in up to 9% of women and 24% of men (19, 20); while the RMMA is much more widespread and occurs in up to 60% of normal population, 80% of these occurring in NREM sleep (21).

While insomnia is defined as sleep initiation or maintenance problem despite adequate circumstances to sleep and having daytime consequences, sleep-related breathing disorders include OSA, central sleep apnea syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder. The diagnosis of OSA in adults requires either presence of signs/symptoms or associated medical/psychiatric history coupled with five or more obstructive respiratory events per hour of sleep. Alternatively, OSA is also diagnosed based on ≥15 obstructive respiratory events per hour, even in the absence of associated symptoms or disorders (18). Central disorders of hypersomnolence are characterized by excessive daytime sleepiness that cannot be attributed to another sleep disorder or abnormalities of circadian rhythm and is often caused by intrinsic CNS abnormalities that control the sleep–wake cycle. Circadian rhythm sleep–wake disorders are defined as a chronic or recurrent pattern of sleep–wake rhythm disruption lasting for at least 3 months. Parasomnias can be either NREM related or REM related and include conditions such as sleep walking, nightmare disorder, sleep enuresis, sleep-related hallucinations, etc. Sleep-related movement disorders are characterized by simple, often stereotyped movements during sleep and include restless legs syndrome, periodic limb movement disorder, SB, benign sleep myoclonus of infancy, etc. SB refers to RMMA characterized by tooth grinding or clenching in sleep that lacks a definitive physiological purpose and is associated with intense sleep arousal activity (22). It is polysomnographically characterized by forceful, short (approximately 250 ms) rhythmic, or prolonged contractions of masticatory muscles (23).

The etiology of sleep disorders can be related to social, psychological, and anatomical factors. Insomnia occurs because of a combination of biological, mental, and social factors, but, stress, old age, and female gender play a major role. OSA occurs due to frequent periods of collapse of the pharyngeal airway. This causes a reduction in oxygen saturation of blood leading to cortical and brainstem arousals. Risk factors for OSA include obesity, male sex, alcoholism, increasing age, etc., and it has been found to be associated with higher incidence of hypertension, myocardial infarction, congestive heart failure, and diabetes (24–27). Narcolepsy and cataplexy have been found to be involved in the presence of HLA-DQB1*0602 haplotype and loss of hypocretin (orexin) producing neurons in the brain (28). The SIDS, a sudden death of infants less than a year old during sleep, is currently the third leading cause of death in infants in the United States (29). The exact cause is still not known but developmental abnormalities of the cardiorespiratory system are one of the proposed etiologies (30). SB can occur due to both central (involving brain neurotransmitters, basal ganglia, limbic system) (31) and peripheral (dental occlusion or other morphological features of jaw system) factors, with central factors being more important (32). Patients of sleep bruxism, a more intense form of RMMA, experience higher episodes of RMMA per hour than patients without bruxism (13). Three types of bruxism have been described: tooth grinding with friction sounds, tooth clenching, and tapping or jaw bracing (33).

LINKAGE OF TCR TO VARIOUS SLEEP DISORDERS

The TCR, as the most powerful autonomic reflex, is known to cause bradycardia and apnea. The resulting decrease in heart rate and apnea are the mechanisms through which the TCR can be implicated in causing various sleep disorders (**Figure 1**). In this regard, the role of peripheral TCR (DR) in causing SIDS has been investigated (6, 11). The rostral trigeminal sensory nuclear complex neurons convey information from orofacial

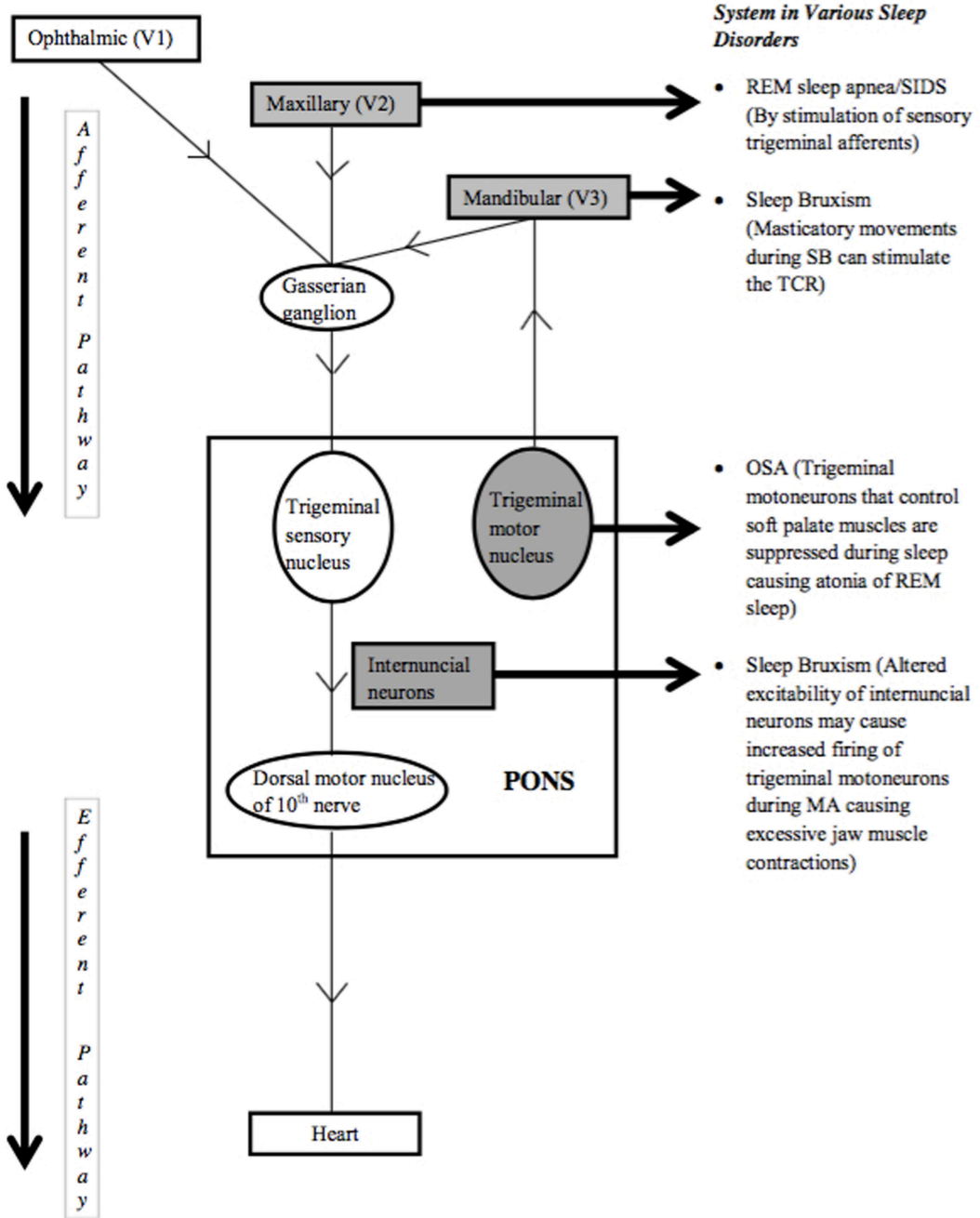

FIGURE 1 | Trigemino-cardiac reflex pathway and sleep disorders.

regions to the thalamus. Cairns et al. have reported suppression of these neurons during active sleep, the exact cause of which is not known, but, is speculated to contribute to maintaining the integrity of active sleep (34). Classical cardiorespiratory changes (bradycardia, apnea, and hypertension) associated with OSA are multifactorial; however, the role of peripheral TCR (DR) in causing such changes cannot be underestimated (35). Interestingly, the TCR can also be linked to both the causation as well as systemic manifestations of OSA. One of the key components of OSA is hypoxemia that itself acts as a potential risk factor for inciting the TCR. Also, hypoxemia is a known cause of sudden death in such patients; therefore may suggest the role of the TCR in victims of sudden death as well (35). Recently, the role of TCR is postulated for the phenomenon of sleep bruxism and thus, the TCR seems to cause a broad range of sleep disorders that are elaborated below in detail.

SLEEP BRUXISM

Heart rate remains stable during normal sleep when breathing is normal. However, when breathing becomes labored due to airway obstruction, the fall in oxygen content of blood causes the body to put extra effort to obtain oxygen, leading to MA of the brain. MA episodes are characterized by tachycardia, increased muscle tone, and increased brain activity, while the person remains asleep (36). Sleeping in the supine position also seems to affect the frequency of SB, probably because this position is associated with airway obstruction (37). Hypotheses postulated for RMMA–SB episodes include a need to increase salivary flow for lubrication during sleep, need to reduce heart rate during MA of the brain, and need to open the airway during episodes of airway collapse (38, 39). Schames et al. in 2012 discussed the physiology of SB and the TCR as a probable cause of SB. The authors have discussed how SB occurs as a result of tachycardia during MA and then stimulates a vagal response (12). SB has been reported to be secondary to MA of the brain earlier by Kato et al. in 2001 (40). A sequence of physiological changes starting with increased respiratory rate, followed by increased EEG activity and an increase in heart rate has been described to occur just before an RMMA episode (41). Schames et al. proposed that tachycardia occurs due to brain MA and probably causes an RMMA–SB episode. Whereas, masticatory movements stimulate the TCR and result in bradycardia, teeth contact occurring during SB serves as an even stronger stimulus for the TCR resulting in more profound bradycardia than RMMA alone (12). Thus, RMMA–SB episodes have been proposed to be an auto-regulatory process occurring during sleep with TCR playing a central role in SB. The fact that partial masticatory movements, as in the submaximal opening of mouth by a spring device, causes prolonged reduction of blood pressure and heart rate has been substantiated by Brunelli et al. (42).

Chase et al. identified neurons in the medullary reticular formation to be responsible for the postsynaptic inhibition of trigeminal motor neurons during active sleep, causing atonia of masseter muscles (43). Another report by Gastaldo et al. suggests the presence of a group of interneurons that modulate the trigeminal motor system. Alteration in the excitability of this group of interneurons could increase the firing probability in trigeminal motor neurons during sleep arousals leading to excessive jaw muscle contractions, as seen in SB (44).

Though the physiology of SB is not exactly known, this above-mentioned available knowledge does point toward the TCR playing an important role in its pathogenesis, but, will need further confirmatory evidence in implicating TCR definitively.

OSA, CENTRAL SLEEP APNEA, SUDDEN DEATH, AND SIDS

Noradrenergic cells in the brainstem are known to project to trigeminal motoneurons which control soft palate muscles, and their discharge activity has been positively correlated with sleep state-dependent changes in muscle tone (45). Schwarz et al. in 2008 demonstrated that noradrenaline plays a modulatory role in potentiating glutamate-dependent synaptic transmission (46). The same authors in 2010 reported that noradrenaline could not trigger motoneuron excitability on its own; instead, it acts to facilitate glutamatergic motor excitation. The glutamatergic drive is reported to be minimal during REM sleep causing the atonia of REM sleep (47), the reason why drugs that increase noradrenergic neurotransmission have had limited success in increasing muscle tone during REM sleep (48). Schwarz and Peever propose that drugs that boost glutamate receptor function in conjunction with noradrenergic agents could be successful in counteracting sleep-related motor suppression, such as that underlying OSA (49). So, the trigeminal system seems to have a role in OSA as well, but whether the TCR is involved or not, needs to be explored.

The naso-trigeminal reflex, a form of peripheral TCR, is known to be a protective response for the upper airways from noxious substances. Dutschmann and Herbert in 1999 tested the hypothesis that stimulation of sensory trigeminal afferents might contribute to REM sleep apnea. They reported that injection of carbachol (mixed agonist for nicotinic and muscarinic acetylcholine receptors) into pontine reticular nuclei of anesthetized rats causes marked potentiation of ethmoidal nerve induced respiratory depression and induces REM sleep like respiratory suppression, even apnea in some cases. The authors speculated that activation of sensory trigeminal afferents during REM sleep could easily trigger centrally mediated apneas and cause pathological conditions like REM sleep apnea or SIDS (50). An increase in upper airway resistance and increased nasal discharge, as seen in allergic rhinitis and rhino sinusitis, have been found responsible for disordered breathing in sleep and MA (51). Tobacco smoke causes congestion and increased nasal airflow resistance. Trigeminal neurons can be activated by mast cell mediators and may contribute to sneezing and itching (52). Trigeminal fibers to the central nervous system convey the sensation of nasal pruritus. The stimulation of nasal trigeminal receptors by factors such as nasal congestion, nasal discharge, or smoke might activate the TCR and may cause sleep disorders. Allergic rhinitis is known to cause neuronal hyper-responsiveness of upper airways to stimuli that activate nasal afferents (53). Nasal inhalation of particulate material or rubbing of inferior turbinate has been shown to cause bronchoconstriction and cardio-depression, through stimulation of trigeminal afferents and activation of TCR (54). A similar response to nasal congestion or nasal discharge by activation of TCR or DR may be caused in allergic rhinitis. Lavie et al. have suggested that increased upper airway resistance and nasal discharge seen in allergic rhinitis cause disordered breathing in sleep and MA (up to 10 times more than in normal controls) (51). Whether these MA episodes are associated with higher incidence of SB in patients of allergic rhinitis needs to be established. Cook et al. observed an exaggerated response to cold stimulus applied on face (simulating DR) in people with non-eosinophilic non-allergic rhinitis (NENAR) as compared to normal individuals (55). There was a significant increase in airway resistance in patients of NENAR due to increase in parasympathetic tone [autonomic control of nasal vasculature (56)] but not in normal individuals. Here, the afferent is mediated by the trigeminal nerve while the efferent limb is parasympathetic. This study observed an exaggerated DR or TCR in individuals with NENAR and thus there may be a possible association of nasal discharge

or congestion and sleep disorders linked through TCR in such individuals. This needs to be explored further. It is well known that OSA may occur in patients with rhinitis and therefore, sleep disorders like OSA or SB might be linked *via* activation of TCR by nasal congestion/discharge or inflammatory triggers. Further research in this direction is warranted.

Heiser et al. have demonstrated that trigeminal stimulation during sleep leads to arousals in a dose- and time-dependent manner (57, 58). Several authors have shown earlier that failure to arouse from sleep could be the causative factor for SIDS. Decreased spontaneous arousals during sleep in SIDS victims compared with control infants has been described (59, 60), and has been attributed to the possible immaturity of the autonomic nervous system as shown by Tuladhar et al. in their study, where they examined heart rate responses to arousing and non-arousing trigeminal stimuli (61). Tuladhar et al. in 2005 also reported that the bradycardia occurring in response to non-arousing stimulation of the trigeminal nerve is present in infants up to 6 months of age and is stronger when sleeping in the supine position and the NREM (quiet sleep) sleep stage (62).

It is a well-established fact that the autonomic nervous system plays a critical role in the pathogenesis of various cardiac arrhythmias (63, 64). For example, atrial fibrillation reportedly has an association with an imbalance between the sympathetic and parasympathetic supply of the heart (65). Similarly, ventricular fibrillation has been shown to be initiated by sympathetic stimulation, especially in an ischemic heart (66). Though sinus arrhythmia is considered physiological during sleep and bradyarrhythmias also can occur due to increased vagal activity (67), especially during NREM sleep, the increased sympathetic drive at the end of sleep can cause adverse events during awakening from sleep (68). Sudden cardiac death occurring due to ventricular arrhythmias, especially ventricular fibrillation, carries a mortality rate of up to 250,000–450,000 per year in the United States (69). OSA-associated hypoxemia results in bradycardia and increased peripheral sympathetic activity resulting in vasoconstriction (70), the same response that occurs during DR. A direct relationship between the severity of OSA and the risk of sudden cardiac death at night has been proposed, probably due to greater number of nocturnal ischemic events in these patients (71). In a recent study on more than 10,000 sleep study of patients, 78% were found to have sleep apnea and during the follow-up of 15 years, they found that 142 (2%) had sudden cardiac arrest, either fatal or resuscitated (72). Though there is no direct linking evidence between the TCR and sudden cardiac death, the amount of influence that the autonomic system exerts on the heart, manifesting either as arrhythmias or as OSA-induced bradycardia and hypertension, does suggest the possibility of the TCR playing a role in sudden death as well.

Based on these reports, the TCR does seem to have a role in various sleep disorders, either due to altered noradrenergic or glutamatergic control, or in the form of naso-trigeminal reflex, or as a result of the immaturity of the autonomic nervous system. It underlines again that the TCR is one of the most important phenomenologies in (clinical) neuroscience.

LIMITATION

This review is not a systematic review. It is more hypothetical in nature and is aimed to postulate the role of TCR in various sleep disorders so that future research could be directed on this important topic.

CONCLUSION

The pathophysiology of sleep disorders like OSA, SB, SD, and SIDS is not entirely understood at this time. Various hypotheses have been proposed for each of these conditions. The TCR might be playing a protective role in the case of sleep bruxism, while an exaggerated form of this reflex could be responsible for SD and SIDS. Based on available literature and exemplary cases, the TCR can be thought of as also playing an important role in various sleep disorders, though further evidence is warranted before it can be definitively implicated.

AUTHOR CONTRIBUTIONS

TC has made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data, and helped in writing the manuscript. BB has participated in data acquisition and interpretation of data and writing the article. GS has participated in drafting and writing the article. BS has participated in developing the concept and writing. All the authors have given final approval for submission of this version.

REFERENCES

1. Reding GR, Rubright WC, Zimmerman SO. Incidence of bruxism. *J Dent Res* (1966) 45:1198–204. doi:10.1177/00220345660450042701
2. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* (1997) 20:705–6.
3. Sandu N, Spiriev T, Lemaitre F, Filis A, Schaller B; Trigemino-Cardiac Reflex Examination Group (TCREG). New molecular knowledge towards the trigemino-cardiac reflex as a cerebral oxygen-conserving reflex. *ScientificWorldJournal* (2010) 10:811–7. doi:10.1100/tsw.2010.71
4. Schaller B, Cornelius JF, Sandu N, Ottaviani G, Perez-Pinzon MA. Oxygen-conserving reflexes of the brain: the current molecular knowledge. *J Cell Mol Med* (2009) 13:644–7. doi:10.1111/j.1582-4934.2009.00659.x
5. Sandu N, Cornelius J, Filis A, Nöthen C, Rasper J, Kulinsky VI, et al. Cerebral hemodynamic changes during the trigeminocardiac reflex: description of a new animal model protocol. *ScientificWorldJournal* (2010) 10:1416–23. doi:10.1100/tsw.2010.136
6. Lemaitre F, Chowdhury T, Schaller B. The trigeminocardiac reflex – a comparison with the diving reflex in humans. *Arch Med Sci* (2015) 11:419–26. doi:10.5114/aoms.2015.50974
7. Meuwly C, Golanov E, Chowdhury T, Erne P, Schaller B. Trigeminal cardiac reflex: new thinking model about the definition based on a literature review. *Medicine (Baltimore)* (2015) 94:e484. doi:10.1097/MD.0000000000000484
8. Sandu N, Sadr-Eshkevari P, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). Usefulness of case reports to improve medical knowledge regarding trigemino-cardiac reflex in skull base surgery. *J Med Case Rep* (2011) 5:149. doi:10.1186/1752-1947-5-149
9. Nöthen C, Sandu N, Prabhakar H, Filis A, Arasho BD, Buchfelder M, et al. Trigemino-cardiac reflex and antecedent transient ischemic attacks. *Expert Rev Cardiovasc Ther* (2010) 8:509–12. doi:10.1586/erc.10.19

10. Schaller B. Trigeminocardiac reflex. A clinical phenomenon or a new physiological entity? *J Neurol* (2004) 251:658–65. doi:10.1007/s00415-004-0458-4
11. Singh GP, Chowdhury T, Bindu B, Schaller B. Sudden infant death syndrome – role of trigeminocardiac reflex: a review. *Front Neurol* (2016) 7:221. doi:10.3389/fneur.2016.00221
12. Schames SE, Schames J, Schames M, Chagall-Gungur SS. Sleep bruxism, an autonomic self-regulating response by triggering the trigeminal cardiac reflex. *J Calif Dent Assoc* (2012) 40:670–1, 674–6.
13. Carskadon MA, Dement WC. Normal human sleep: an overview. 5th ed. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. St. Louis: Elsevier Saunders (2005). p. 16–26.
14. Smith C, Lapp L. Increases in number of REMs and REM density in humans following an intensive learning period. *Sleep* (1991) 14:325–30.
15. Madsen PL, Schmidt JF, Wildschiødtz G, Friberg L, Holm S, Vorstrup S, et al. Cerebral O_2 metabolism and cerebral blood flow in humans during deep and rapid-eye movement sleep. *J Appl Physiol* (1991) 70:2597–601.
16. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* (1993) 328:303–7. doi:10.1056/NEJM199302043280502
17. Colten HR, Altevogt BM, editors. Sleep physiology. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington: National Academies Press (2006). p. 33–54.
18. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* (2014) 146:1387–94. doi:10.1378/chest.14-0970
19. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med* (1998) 157:144–8. doi:10.1164/ajrccm.157.1.9706079
20. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* (2001) 163:608–13. doi:10.1164/ajrccm.163.3.9911064
21. Lavigne GJ, Rompre PH, Poirier G, Huard H, Kato T, Montplaisir JY. Rhythmic masticatory muscle activity during sleep in humans. *J Dent Res* (2001) 80:443–8. doi:10.1177/00220345010800020801
22. Kato T, Montplaisir JY, Guitard F, Sessle BJ, Lund JP, Lavigne GJ. Evidence that experimentally induced sleep bruxism is a consequence of transient arousal. *J Dent Res* (2003) 82:284–8. doi:10.1177/154405910308200408
23. Lavigne GJ, Rompré PH, Montplaisir JY. Sleep bruxism: validity of clinical research diagnostic criteria in a controlled polysomnographic study. *J Dent Res* (1996) 75:546–52. doi:10.1177/00220345960750010601
24. Young T, Javaheri S. Systemic and pulmonary hypertension in obstructive sleep apnea. 4th ed. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. Philadelphia: Elsevier Saunders (2005). p. 1192–202.
25. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* (2005) 365:1046–53. doi:10.1016/S0140-6736(05)71141-7
26. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* (1998) 97:2154–9. doi:10.1161/01.CIR.97.21.2154
27. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* (2004) 160:521–30. doi:10.1093/aje/kwh261
28. Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* (2000) 6:991–7. doi:10.1038/79690
29. CDC. *Sudden Infant Death Syndrome (SIDS) [Online]* (2006). Available from: http://www.cdc.gov/sids/data.htm
30. Verrier RL, Josephson ME. Cardiac arrhythmogenesis during sleep: mechanisms, diagnosis, and therapy. 4th ed. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. Philadelphia: Elsevier Saunders (2005). p. 1171–91.
31. Lavigne GJ, Kato T, Kolta A, Sessle BJ. Neurobiological mechanisms involved in sleep bruxism. *Crit Rev Oral Biol Med* (2003) 14:30–46. doi:10.1177/154411130301400104
32. Lobbezoo F, Naeije M. Bruxism is mainly regulated centrally, not peripherally. *J Oral Rehabil* (2001) 28:1085–91. doi:10.1046/j.1365-2842.2001.00839.x
33. Vetrugno R, Provini F, Plazzi G, Lombardi C, Liguori R, Lugaresi E, et al. Familial nocturnal facio-mandibular myoclonus mimicking sleep bruxism. *Neurology* (2002) 58:644–7. doi:10.1212/WNL.58.4.644
34. Cairns BE, Fragoso MC, Soja PJ. Activity of rostral trigeminal sensory neurons in the cat during wakefulness and sleep. *J Neurophysiol* (1995) 73:2486–98.
35. Ludka O, Konecny T, Somers V. Sleep apnea, cardiac arrhythmias, and sudden death. *Tex Heart Inst J* (2011) 38:340–3.
36. Huynh N, Kato T, Rompré PH, Okura K, Saber M, Lanfranchi PA, et al. Sleep bruxism is associated to micro-arousals and an increase in cardiac sympathetic activity. *J Sleep Res* (2006) 15:339–46. doi:10.1111/j.1365-2869.2006.00536.x
37. Miyawaki S, Lavigne GJ, Pierre M, Guitard F, Montplaisir JY, Kato T. Association between sleep bruxism, swallowing-related laryngeal movement, and sleep positions. *Sleep* (2003) 26:461–5.
38. Thie NM, Kato T, Bader G, Montplaisir JY, Lavigne GJ. The significance of saliva during sleep and the relevance of oromotor movements. *Sleep Med Rev* (2002) 6:213–27. doi:10.1053/smrv.2001.0183
39. Landry M, Rompre PH, Manzini C, Guitard F, de Grandmont P, Lavigne GJ. Reduction of sleep bruxism using a mandibular advancement device: an experimental controlled study. *Int J Prosthodont* (2006) 19:549–56.
40. Kato T, Rompre PH, Montplaisir JY, Sessle BJ, Lavigne GJ. Sleep bruxism: an oromotor activity secondary to micro-arousal. *J Dent Res* (2001) 80:1940–4. doi:10.1177/00220345010800101501
41. Lavigne GJ, Huynh N, Kato T, Okura K, Adachi K, Yao D, et al. Genesis of sleep bruxism: motor and autonomic-cardiac interactions. *Arch Oral Biol* (2007) 52:381–4. doi:10.1016/j.archoralbio.2006.11.017
42. Brunelli M, Coppi E, Tonlorenzi D, Del Seppia C, Lapi D, Colantuoni A, et al. Prolonged hypotensive and bradycardic effects of passive mandibular extension: evidence in normal volunteers. *Arch Ital Biol* (2012) 150:231–7. doi:10.4449/aib.v150i4.1420
43. Chase MH, Enomoto S, Hiraba K, Katoh M, Nakamura Y, Sahara Y, et al. Role of medullary reticular neurons in the inhibition of trigeminal motoneurons during active sleep. *Exp Neurol* (1984) 84:364–73. doi:10.1016/0014-4886(84)90233-4
44. Gastaldo E, Quatrale R, Graziani A, Eleopra R, Tugnoli V, Tola MR, et al. The excitability of the trigeminal motor system in sleep bruxism: a transcranial magnetic stimulation and brainstem reflex study. *J Orofac Pain* (2006) 20:145–55.
45. Chan E, Steenland HW, Liu H, Horner RL. Endogenous excitatory drive modulating respiratory muscle activity across sleep-wake states. *Am J Respir Crit Care Med* (2006) 174:1264–73. doi:10.1164/rccm.200605-597OC
46. Schwarz PB, Yee N, Mir S, Peever JH. Noradrenaline triggers muscle tone by amplifying glutamate-driven excitation of somatic motoneurones in anaesthetized rats. *J Physiol* (2008) 586:5787–802. doi:10.1113/jphysiol.2008.159392
47. Burgess CR, Lai D, Siegel J, Peever J. An endogenous glutamatergic drive onto somatic motoneurons contributes to the stereotypical pattern of muscle tone across the sleep-wake cycle. *J Neurosci* (2008) 28:4649–60. doi:10.1523/JNEUROSCI.0334-08.2008
48. Horner RL. Respiratory motor activity: influence of neuromodulators and implications for sleep disordered breathing. *Can J Physiol Pharmacol* (2007) 85:155–65. doi:10.1139/y06-089
49. Schwarz PB, Peever JH. Noradrenergic control of trigeminal motoneurons in sleep: relevance to sleep apnea. *Adv Exp Med Biol* (2010) 669:281–4. doi:10.1007/978-1-4419-5692-7_57
50. Dutschmann M, Herbert H. Pontine cholinergic mechanisms enhance trigeminally evoked respiratory suppression in the anesthetized rat. *J Appl Physiol* (1999) 87:1059–65.
51. Lavie P, Gertner R, Zomer J, Podoshin L. Breathing disorders in sleep associated with "microarousals" in patients with allergic rhinitis. *Acta Otolaryngol* (1981) 92:529–33. doi:10.3109/00016488109133292
52. Naclerio RM, Bachert C, Baraniuk JN. Pathophysiology of nasal congestion. *Int J Gen Med* (2010) 3:47–57. doi:10.2147/IJGM.S8088
53. Canning BJ. Neurology of allergic inflammation and rhinitis. *Curr Allergy Asthma Rep* (2002) 2:210–5. doi:10.1007/s11882-002-0021-2

54. Baraniuk JN, Merck SJ. Nasal reflexes: implications for exercise, breathing and sex. *Curr Allergy Asthma Rep* (2008) 8:147–53. doi:10.1007/s11882-008-0025-7
55. Cook JA, Hamilton JW, Jones AS. The diving reflex in non-eosinophinic non-allergic rhinitis. *Clin Otolaryngol Allied Sci* (1996) 21:226–7. doi:10.1111/j.1365-2273.1996.tb01730.x
56. Anggård A. Parasympathetic influence on the nasal mucosa. *Acta Otolaryngol* (1977) 83:22–4. doi:10.3109/00016487709128806
57. Heiser C, Baja J, Lenz F, Sommer JU, Hörmann K, Herr RM, et al. Trigeminal induced arousals during human sleep. *Sleep Breath* (2015) 19:553–60. doi:10.1007/s11325-014-1046-1
58. Stuck BA, Stieber K, Frey S, Freiburg C, Hörmann K, Maurer JT, et al. Arousal responses to olfactory or trigeminal stimulation during sleep. *Sleep* (2007) 30:506–10. doi:10.1093/sleep/30.4.506
59. Kahn A, Groswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, et al. Sleep and cardiorespiratory characteristics of infant victims of sudden infant death: a prospective case-control study. *Sleep* (1992) 15:287–92.
60. Schechtman VL, Harper RM, Wilson AJ, Southall DP. Sleep state organization in normal infants and victims of the sudden infant death syndrome. *Pediatrics* (1992) 89:865–70.
61. Tuladhar R, Harding R, Michael Adamson T, Horne RS. Comparison of postnatal development of heart rate responses to trigeminal stimulation in sleeping preterm and term infants. *J Sleep Res* (2005) 14:29–36. doi:10.1111/j.1365-2869.2004.00434.x
62. Tuladhar R, Harding R, Adamson TM, Horne RS. Heart rate responses to non-arousing trigeminal stimulation in infants: effects of sleep position, sleep state and postnatal age. *Early Hum Dev* (2005) 81:673–81. doi:10.1016/j.earlhumdev.2005.04.002
63. Harris AS, Estandia A, Tillotson RF. Ventricular ectopic rhythms and ventricular fibrillation following cardiac sympathectomy and coronary occlusion. *Am J Physiol* (1951) 165:505–12.
64. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res* (2014) 114:1004–21. doi:10.1161/CIRCRESAHA.113.302549
65. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation* (2002) 105:2753–9. doi:10.1161/01.CIR.0000018443.44005.D8
66. Opthof T, Misier AR, Coronel R, Vermeulen JT, Verberne HJ, Frank RG, et al. Dispersion of refractoriness in canine ventricular myocardium. Effects of sympathetic stimulation. *Circ Res* (1991) 68:1204–15. doi:10.1161/01.RES.68.5.1204
67. Verrier RL, Josephson ME. Impact of sleep on arrhythmogenesis. *Circ Arrhythm Electrophysiol* (2009) 2:450–9. doi:10.1161/CIRCEP.109.867028
68. Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, et al. Circadian variation in the frequency of sudden cardiac death. *Circulation* (1987) 75:131–8. doi:10.1161/01.CIR.75.1.131
69. Lloyd-Jones D, Adams RJ, Brown TM, Brown TM, Carnethon M, Dai S, et al. Heart disease and stroke statistics – 2010 update: a report from the American Heart Association. *Circulation* (2010) 121:e46–215. doi:10.1161/CIRCULATIONAHA.109.192667
70. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* (1995) 96:1897–904. doi:10.1172/JCI118235
71. Kuniyoshi FH, Garcia-Touchard A, Gami AS, Romero-Corral A, van der Walt C, Pusalavidyasagar S, et al. Day-night variation of acute myocardial infarction in obstructive sleep apnea. *J Am Coll Cardiol* (2008) 52:343–6. doi:10.1016/j.jacc.2008.04.027
72. Gami AS, Olson EJ, Shen WK, Wright RS, Ballman KV, Hodge DO, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10.701 adults. *J Am Coll Cardiol* (2013) 62:610–6. doi:10.1016/j.jacc.2013.04.080

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Chronic Trigemino-Cardiac Reflex: An Underestimated Truth

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The trigemino-cardiac reflex (TCR) is a brainstem reflex that manifests as adverse cardiorespiratory events upon the stimulation of sensory branches of the fifth cranial nerve. This reflex is mainly investigated in different neurosurgical procedures and intervention. This reflex is commonly considered as an acute and mild physiological response. On the other hand, more devastating and chronic nature of this reflex is largely underreported and unknown. Therefore, this article aims to provide the comprehensive understanding of the chronic form of TCR, its manifestations, and management by literature search. Also, this paper would certainly impart a better diagnosis and understanding of TCR phenomenon by knowing the relatively less common form of a chronic TCR. This will help thousands and thousands of patients who are still in the phase of diagnosis and are suffering from vague symptoms related to this reflex.

Keywords: trigemino-cardiac reflex, bradycardia, chronic, management, diagnosis

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INTRODUCTION

The trigemino-cardiac reflex (TCR) is a well-established neurogenic reflex that is mainly investigated in neurosurgical patients (1–6). This unique brainstem reflex is incited by the stimulation of the fifth nerve and produces adverse cardiorespiratory changes including bradycardia, asystole, and apnea. Interestingly, the TCR phenomenon reported in the literature mainly reveals the acute as well as transient nature of this reflex that is considered as a mild physiological response in most of the cases (3, 6). Also, the general management of such situations is the removal of stimuli (3, 6, 7). This relatively high prevalence of detection of the TCR occurrences and the relatively often benign course of the phenomenon is owing to the pre-, peri-, and postoperative presence of the anesthetists (1–9).

However, the chronic nature of TCR event is largely underestimated and underreported in the current literature. This may be partly due to the persistent yet vague nature of symptoms (opposite to the acute TCR episode) that make the diagnosis very difficult. An extrapolation of the prevalence from acute to chronic cases suggests that there might also be a substantial number of chronic cases (10). Therefore, this article aims to provide the comprehensive understanding of the chronic form of TCR, its manifestations, and management by literature search. Also, this paper would certainly impart a better diagnosis and understanding of TCR phenomenon by knowing the relatively less common form of a chronic TCR.

METHOD

We searched PubMed for following terms in various combination including ("prolonged" OR "chronic" OR "persistent" OR "delayed") AND ("oculocardiac reflex" OR "trigeminal cardiac reflex"

OR "trigeminocardiac reflex") from January 1, 1970, to August 31, 2016.

Definition of Chronic TCR/OCR

Two criteria define chronic TCR. First, TCR/OCR should be explained by the classic definition of this reflex as defined by our previous work (9). The TCR is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea, or gastric hypermotility during stimulation of any of the sensory branches of the trigeminal nerve. A TCR should include a decrease in heart rate (HR) and mean arterial blood pressure of more than 20% as compared with baseline values before application of the stimulus and should coincide with the surgical manipulation at or around any branches of the trigeminal nerve (9).

Second, chronicity is defined as any TCR/OCR episodes that persisted at least 1 day before or after the surgery or the first insult.

Peripheral and Central TCR

OCR and maxilla–mandibular (MCR) TCRs are categorized as peripheral TCR, and any TCR episode due to the stimulation of the fifth nerve pathway beyond the Gasserian ganglion is considered as the central TCR.

Inclusion

The papers that clearly defined TCR or OCR or MCR as the cause of cardiorespiratory changes were included. All the patients irrespective of age and sex were included. Those papers regardless of the type that has been entirely written in the English language were included. All the relevant cross references were also carefully screened. Pediatric age is defined as the age of less than 18 years.

Exclusion Criteria

The TCR/OCR episodes that occurred only during the surgical manipulation or within 24 h of surgical stimulation or primary insult were considered as acute TCR and excluded.

RESULTS

Total of 140 articles were searched through applying the terms. Out of 140, 93 articles met the language and human subject restrictions. Out of 93, only 6 articles finally met the inclusion criteria and further reviewed. Total of six patients included in the final analysis (**Table 1**). Out of six, 50% were pediatric patients. Strikingly, all the six reported patients were male. Further analysis revealed that the five out of six patients were related to peripheral TCR group and remaining one showed central TCR phenomenon. The timing of presentation of the chronic TCR varied from 29 h to several years. The description of cases is given below.

The Central TCR Case

This was an octogenarian male patient who underwent a microvascular decompression for a trigeminal neuralgia and developed multiple episodes of bradycardia in postoperative period, and these intermittent adverse cardiovascular changes persisted for several days (11). This patient also developed an event of cardiac arrest and was resuscitated with chest compressions. He was further managed with a temporary pacemaker. Notably, his cardiovascular perturbations coincided with episodes of facial pain. Eventually, he underwent a radiofrequency ablation of fifth nerve and all his cardiovascular and pain related symptoms improved. Strikingly, there were no episodes of such hemodynamics disturbances in the intraoperative period.

The Peripheral TCR Cases

There were five patients with reported chronic peripheral TCR. In the *first case*, a 13-year-old boy had an orbit medial wall blowout fracture and presented with worsening of nausea and bradycardia 29 h of first insult (12). These symptoms coincided with gazing on rightward direction. An emergency operation was performed, and symptoms got improved after that. In the *second case*, a 12-year-old boy presented with nausea/vomiting and bradycardia (56/min) that intermittently persisted for 72 h after the initial injury (13). He was diagnosed as a case of orbit medial wall blowout fracture. Same day operation was done, and patient's all symptoms as well as the HR got normalized (68/min). In *the third case*, a 17-year-old male victim of a gunshot at orbit (globe perforation with a foreign body) developed severe bradycardia 48 h after globe perforation repair and persisted for 6 days when a temporary pacemaker was put and eventually foreign body was removed (14). Hemodynamic symptoms reverted to normal. In the *fourth case*, an adult patient who had an orbital floor fracture showed symptoms of nausea, dizziness, bradycardia, sleep disturbances after 1 month of the initial insult (15). He also underwent an operation, and his symptoms got improved. In the *fifth case*, a 56-year-old

TABLE 1 | Cases of chronic trigemino-cardiac reflex.

S no.	Age/gender	injury/procedure	Hemodynamics	Duration	Management	Outcome
1	82/M	MVD of V CN	Bradycardia, cardiac arrest	Several days	Temporary pacemaker Radiofrequency ablation	Improved
2	13/M	Orbital fracture	Bradycardia	29 h	Surgery	Improved
3	12/M	Orbital fracture	Bradycardia	72 h	Surgery	Improved
4	17/M	Foreign body and globe perforation	Bradycardia	48 h	Temporary pacemaker Surgery	Improved
5	Adult/M	Orbital fracture	Bradycardia	1 month	Surgery	Improved
6	56/M	Foreign body in orbit	Bradycardia	40 years	Surgery	Improved

SN, serial number; MVD of V CN, microvascular decompression of fifth cranial nerve; M, male.

male war victim presented with features of nausea, vomiting, dyspnea, and bradycardia, 40 years (evisceration was done) after the primary insult (16). At this time, CT scan revealed foreign body in orbit and removed surgically, that completely resolved the symptoms.

DISCUSSION

The TCR is one of the most investigated brainstem reflexes that manifests commonly as adverse hemodynamic changes during the stimulation of any of the sensory branch of the trigeminal nerve. This phenomenon has been reported in various surgical conditions as well as in neurosurgical interventions and mainly illustrates the acute nature of this reflex that persists during the surgical and other chemical/physical/electrical stimuli (1–10). The afferent nerve fibers carry the stimulus *via* the trigeminal nerve and efferent fibers through the vagus nerve. The TCR is broadly classified as the peripheral and the central type depending upon the stimulation of anatomical location. Depending upon the three sensory divisions of the trigeminal nerve, the peripheral type is further divided into OCR and MCR (9). After reviewing the literature, one can infer that the TCR is a mild transient physiological response and gets abolished after the removal of the inciting stimulus. However, as mentioned in the above-described cases, it can be clearly seen that this phenomenon also has a chronic type and that has far more impact in overall symptomatology and clinical decision-making. We have now gone outside the OR and open the window from a strict cause-effect relationship within a few seconds to a wider variance of reactions (10, 17). Our previous definition work is based on acute cases. We have to look now if these works are also available for the chronic cases. Another point is the connection of chronic TCR to the oxygen-conserving reflex (8). Again, we have no cases of cerebral ischemia undermining a strong correlation between these two phenomena.

Trigemino-cardiac reflex versus vasovagal: the vasovagal response (VVR) can also be postulated as the one of the mechanisms responsible for the similar autonomic manifestations. This reflex mainly controlled through two pathways (18). One is the central VVR that involves cortico-hypothalmic and medullary cardiac centers and second is the peripheral VVR that included heart directly. The VVR is commonly incited by intense emotion, prolonged standing, instrumentation, and severe pain responses (18, 19). This is a transient phenomenon, which improves quickly on lying down, and is usually found in healthy individuals. In described cases, none of the above mentioned inciting factors were present exclusively. In addition, these autonomic manifestations were improved after the surgical interventions, thereby, clearly describes the cause-effect relationship of TCR phenomenon.

There are three significant findings in this review about chronic TCR (11–16). First, the peripheral TCR was the commonest type, and the OCR was the most common subtype associated with the chronic form of TCR. Whether or not the ophthalmic division of the fifth nerve is more prone to the chronic form of TCR is a matter of further investigation. However, considering the present findings of this review, it seems plausible. Also, the first branch of the fifth nerve is also the shortest and pure sensory branch that may be a factor of more incidence of peripheral TCR episodes. Second, besides bradycardia, nausea was the commonest presenting symptom. It is apparent that because of vague symptoms (nausea, vomiting, etc.), the diagnosing the chronic TCR is very challenging. Therefore, it could be another reason for the underreported incidence of chronic TCR cases. Therefore, we want to emphasize here that the TCR should also be included in the differential diagnosis of the patient, if he/she presents with vague symptoms such as nausea, vomiting, dizziness, etc. and had a history of injury (even trivial) including eye, orbit, or any other structure supplied by the fifth nerve. Thirdly, in all the cases, the surgery was the definitive cure for all the symptoms related to the TCR. This important finding suggests that the chronic form of TCR seems more like a pathological rather than a physiological entity, and has a negative impact on the overall health of the patient. Here, it should be noted that the indication of surgery/intervention was mainly due to the on-going symptoms rather than an absolute pathological or surgical cause. Therefore, for the entire medical community, it is imperative to understand the phenomenon of chronic TCR that is not limited to any particular specialty. This will help thousands and thousands of patients who are still in the phase of diagnosis and are suffering from those vague symptoms daily.

LIMITATION

In the paucity of substantial evidence, these case reports should only be interpreted as an informative tool for understanding the concept of chronic TCR. These cases do exhibit a sound cause and effect relationship and therefore support our hypothesis. All cases were found in males. It may be a simple reflection of injury pattern that is more common in the male gender (20). Whether or not peripheral TCR is common in males is a matter of further research.

CONCLUSION

The chronic form of TCR is an underreported entity and certainly has a substantial impact on the patient health. With the knowledge of the chronic TCR, we can be certainly able to diagnose more and more patients and impart better management in such cases. Further research is warranted to elucidate the exact mechanism of chronic TCR.

AUTHOR CONTRIBUTIONS

TC helped in developing the concept, designing, data collection, data interpretation, and writing the manuscript. BS gave substantial inputs in developing the concept and writing the manuscript. Both the authors accepted the final version.

REFERENCES

1. Schaller B, Probst R, Strebel S, Gratzl O. Trigeminocardiac reflex during surgery in the cerebellopontine angle. *J Neurosurg* (1999) 90:215–20. doi:10.3171/jns.1999.90.2.0215
2. Chowdhury T, Sandu N, Meuwly C, Cappellani RB, Schaller B. Trigeminal cardiac reflex: differential behavior and risk factors around the course of the trigeminal nerve. *Future Neurol* (2014) 9:41–7. doi:10.2217/fnl.13.62
3. Chowdhury T, Sandu N, Meuwly C, Schaller B. Trigeminal cardiac reflex: current trends. *Expert Rev Cardiovasc Ther* (2014) 12(1):9–11. doi:10.1586/14779072.2014.862498
4. Chowdhury T, Meuwly C, Sandu N, Schaller B, Cappellani RB. Coronary spasm in neurosurgical patients and role of trigemino-cardiac reflex: a review. *Neurol Res Int* (2014) 2014:5. doi:10.1155/2014/974930
5. Schaller B. Trigeminocardiac reflex. *J Neurol* (2004) 251:658–65. doi:10.1007/s00415-004-0458-4
6. Chowdhury T, Mendelowitz D, Govlanov E, Spiriev T, Belachew A, Sandu N, et al. Trigeminocardiac reflex: an update of the current clinical and physiological knowledge. *J Neurosurg Anesthesiol* (2015) 27(2):136–47. doi:10.1097/ANA.0000000000000065
7. Arasho B, Sandu N, Spiriev T, Prabhakar H, Schaller B. Management of the trigeminocardiac reflex. Facts and own experience. *Neurol India* (2009) 57:375–80. doi:10.4103/0028-3886.55577
8. Schaller B, Buchfelder M. Trigemino-cardiac reflex: a recently discovered "oxygen-conserving" response? The potential therapeutic role of a physiological reflex. *Arch Med Sci* (2006) 2:3–5.
9. Meuwly C, Golanov E, Chowdhury T, Erne P, Schaller B. Trigemino cardiac reflex: new thinking model about the definition based on a literature review. *Medicine (Baltimore)* (2015) 94(5):e484. doi:10.1097/MD.0000000000000484
10. Sandu N, Sadr-Eshkevari P, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). Usefulness of case reports to improve medical knowledge regarding trigemino-cardiac reflex in skull base surgery. *J Med Case Rep* (2011) 5:1–3. doi:10.1186/1752-1947-5-149
11. Hemmer LB, Afifi S, Koht A. Trigeminocardiac reflex in the postanesthesia care unit. *J Clin Anesth* (2010) 22(3):205–8. doi:10.1016/j.jclinane.2009.03.017
12. Kosaka M, Sakamoto T, Yamamichi K, Yamashiro Y. Different onset pattern of oculocardiac reflex in pediatric medial wall blowout fractures. *J Craniofac Surg* (2014) 25(1):247–52. doi:10.1097/SCS.0000000000000408
13. Jurdy L, Malhotra R. White-eyed medial wall blowout fracture mimicking head injury due to persistent oculocardiac reflex. *J Craniofac Surg* (2011) 22(5):1977–9. doi:10.1097/SCS.0b013e31822eaa25
14. Yilmaz T, Erol FS, Yakar H, Köhle U, Akbulut M, Faik Ozveren M. Delayed trigeminocardiac reflex induced by an intraorbital foreign body. Case report. *Ophthalmologica* (2006) 220(1):65–8. doi:10.1159/000089277
15. Chowdhury T, Cappellani RB, Schaller B. Chronic trigemino-cardiac reflex in patient with orbital floor fracture: role of surgery and first description. *J Neurosurg Anesthesiol* (2014) 26(1):91–2. doi:10.1097/ANA.0b013e3182a1a691
16. Yang HS, Oh DE. A case of delayed oculocardiac reflex induced by an intraorbital foreign body. *Ophthal Plast Reconstr Surg* (2011) 27(1):e2–4. doi:10.1097/IOP.0b013e3181d644f4
17. Sandu N, Chowdhury T, Schaller B; Trigemino-Cardiac Reflex Examination Group (TCREG). How to apply case reports in clinical practice using surrogate models via example of the trigeminocardiac reflex. *J Med Case Reports* (2016) 10:84. doi:10.1186/s13256-016-0849-z
18. van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci (Lond)* (1991) 81(5):575–86. doi:10.1042/cs0810575
19. Lambert E, Lambert GW. Sympathetic dysfunction in vasovagal syncope and the postural orthostatic tachycardia syndrome. *Front Physiol* (2014) 5:280. doi:10.3389/fphys.2014.00280
20. Phan LT, Jordan Piluek W, McCulley TJ. Orbital trapdoor fractures. *Saudi J Ophthalmol* (2012) 26(3):277–82. doi:10.1016/j.sjopt.2012.05.008

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MINI REVIEW
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Sudden Infant Death Syndrome – Role of Trigeminocardiac Reflex: A Review

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Sudden infant death syndrome (SIDS) is an unexplained death in infants, which usually occurs during sleep. The cause of SIDS remains unknown and multifactorial. In this regard, the diving reflex (DR), a peripheral subtype of trigeminocardiac reflex (TCR), is also hypothesized as one of the possible mechanisms for this condition. The TCR is a well-established neurogenic reflex that manifests as bradycardia, hypotension, apnea, and gastric hypermotility. The TCR shares many similarities with the DR, which is a significant physiological adaptation to withstand hypoxia during apnea in many animal species including humans in clinical manifestation and mechanism of action. The DR is characterized by breath holding (apnea), bradycardia, and vasoconstriction, leading to increase in blood pressure. Several studies have described congenital anomalies of autonomic nervous system in the pathogenesis of SIDS such as hypoplasia, delayed neuronal maturation, or decreased neuronal density of arcuate nucleus, hypoplasia, and neuronal immaturity of the hypoglossal nucleus. The abnormalities of autonomic nervous system in SIDS may explain the role of TCR in this syndrome involving sympathetic and parasympathetic nervous system. We reviewed the available literature to identify the role of TCR in the etiopathogenesis of SIDS and the pathways and cellular mechanism involved in it. This synthesis will help to update our knowledge and improve our understanding about this mysterious, yet common condition and will open the door for further research in this field.

Keywords: sudden infant death syndrome, trigeminocardiac reflex, diving reflex, oxygen-conserving reflex, bradycardia, asystole, smoking, prenatal nicotine exposure

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INTRODUCTION

Sudden infant death syndrome (SIDS) is defined as the sudden unexplained death of a seemingly healthy child less than 1 year of age, usually during sleep. For the diagnosis of SIDS, the death should remain unexplained even after the autopsy, investigation of mortality scene, and review of clinical history (1). SIDS remains a leading cause of death in infants between ages of 1 month and 1 year. The incidence of SIDS varies between regions and among racial and ethnic subgroups (2, 3). It is a multifactorial disorder, the cause of which is still not fully elucidated. The exact cause of death in SIDS remains unclear; however, the exaggeration of parasympathetic activity and cardiorespiratory response to hypoxia has been suggested as a possible underlying mechanism (4–9). In addition, postnatal age, gestational age at birth, and level of arousability are also linked with SIDS (10, 11).

Infants who succumb to SIDS typically experience a severe bradycardia, which is the most shared and predictive event in infants monitored for life-threatening incidents (12, 13). It may be preceded or is accompanied by centrally mediated apnea. Such abnormal and exaggerated response to sensory trigeminal nerve stimulation has also been implicated in the etiopathogenesis of SIDS (14, 15).

Stimulation of trigeminal nerve leads to consecutive reflex bradycardia, hypotension, apnea, and gastric hypermotility, commonly known as the trigeminocardiac reflex (TCR). This reflex is most often transient, but sometimes may be pronounced and sustainable, particularly, in infants. The diving reflex (DR) (a subtype of TCR) is triggered as a result of stimulation of one of the sensory branches of the trigeminal nerve and leads to inhibition of cardiorespiratory center, thereby causes bradycardia and apnea (16–19). An exaggerated response to hypoxia (i.e., augmented TCR response) causing lethal bradycardia and apnea can be accused of sudden death in the victims of SIDS. In this article, we reviewed the available literature on SIDS to identify the evidence and explore the role of TCR in the pathogenesis of SIDS.

TRIGEMINOCARDIAC REFLEX

Trigeminocardiac reflex has been classified into various subtypes including central, peripheral, and ganglionic TCR (17, 20–24). The central TCR is triggered by the stimulation of the intracranial part of trigeminal nerve proximal to Gasserian ganglion, and the peripheral TCR is triggered by the stimulation of the ophthalmic, maxillary, or mandibular branches of trigeminal nerve (25–30). TCR triggered due to the direct stimulation of Gasserian ganglion is classified as a separate entity (19).

PATHWAY OF TCR

The branches of the trigeminal nerve, Gasserian ganglion, the sensory nucleus of the trigeminal nerve forms the afferent pathway of the reflex (26, 31–33) (**Figure 1**). The short internuncial nerve fibers of the reticular formation connect the afferent pathway to the efferent pathway, which is predominantly formed by the parasympathetic neurons of the dorsal motor nucleus of the vagus nerve and nucleus ambiguus (19). Animal studies have shown the involvement of several other brainstem nuclei in the TCR pathway, which includes trigeminal nucleus caudalis, paratrigeminal nucleus, parabrachial nucleus, rostral ventrolateral medulla oblongata, and dorsal medullary reticular field (34–36). Also, various subtypes of TCR show a difference in their reflex arc. While peripherally originated TCR is relayed *via* the spinal nucleus of the trigeminal nerve to the Kölliker–Fuse nucleus, the centrally originated TCR is conveyed *via* the nucleus of the solitary tract to the lateral parabrachial nucleus (35).

Activation of the sympathetic nervous system has been implicated for the other less common manifestations of TCR, such as tachycardia and hypertension, which are seen in some subtypes of TCR. Studies have revealed that stimulation of the anterior ethmoidal nerve in the nasal mucosa (peripheral TCR) may simultaneously activate the sympathetic and vagal responses. This may result in parasympathetically mediated bradycardia along with sympathetically mediated peripheral vasoconstriction and hypertension (37, 38). In contrast to this, the centrally stimulated TCR manifests as bradycardia and hypotension due to activation of cardioinhibitory vagal response, whereas the ganglionic TCR is clinically present as either increase or decrease in heart rate (bradycardia/tachycardia) and blood pressure (hypotension/hypertension) (39). These varied presentations of TCR are due to co-activation of parasympathetic and sympathetic nervous system (39).

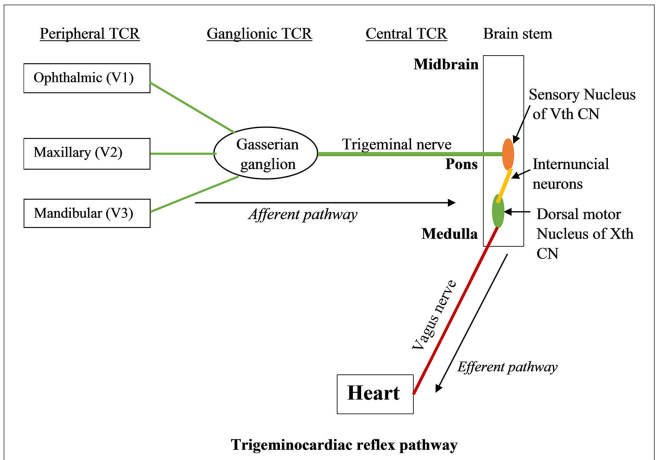

FIGURE 1 | The trigeminocardiac reflex pathway.

DIVING REFLEX AS A SUBTYPE OF TCR

The DR is a powerful autonomic reflex that manifests as the reflex bradycardia, apnea, peripheral vasoconstriction, and hypertension triggered by submersion of a face in cold water through branches of the trigeminal nerve (40). Both TCR and DR are phylogenetically oxygen-conserving reflexes, and researchers reveal a similar reflex arch in both (41). Thus, DR appears to be another subtype of TCR (39). The difference between DR and peripheral TCR shows different effect on blood pressure. Although peripheral TCR causes normotension or hypotension, DR leads to hypertension. This is due to intense peripheral vasoconstriction caused by more strong sympathetic stimulation during DR than during peripheral TCR (42). This reflex also persists in humans and is probably inherited from diving birds and amphibians (18, 32, 43–45). It is particularly prominent in infants and manifests as severe bradycardia upon a single submersion of the face in the water (46, 47). Activation of this reflex due to the stimulation of sensory trigeminal fibers over the face and nasal mucosa causes apnea, a sudden drop in heart rate (due to parasympathetic activation), and a gradual increase in blood pressure as a result of peripheral vasoconstriction (due to increase in sympathetic tone) (44, 45). Also, there is a contraction of spleen releasing erythrocytes in the circulation (48, 49). Thus, the blood flow is redirected to vital organs (the brain and the heart) from the periphery and visceral organs. The heart rate is reduced, thereby lowering O_2 requirement of myocardium and the blood flow to the brain is increased without an increase in the cerebral metabolic oxygen

demand. Thus, DR is a protective oxygen-conserving reflex (18, 32, 44, 45). However, an exaggerated response that results in profound bradycardia can sometimes prove harmful or even fatal (14, 15, 50) and is often said to be associated with sudden death in infants.

ROLE OF TCR IN SUDDEN INFANT DEATH SYNDROME

Sudden infant death syndrome is the leading cause of death in the postneonatal period (12, 13, 51, 52). The exaggeration of parasympathetic activity and cardiorespiratory response to hypoxia has been suggested as the possible mechanism for these events (4–9). Similarly, trigeminal air-stream stimulation (TAS) model also showed that the TAS may induce apnea and bradycardia in premature infants (53). In infants monitored for apparent life-threatening events, severe bradycardia was the most prevalent and predictive event seen in infants who succumbed to SIDS (12, 13, 54), and hypoxia is a frequent event that precedes death in infants of SIDS (55).

Interestingly, the laryngeal chemo-reflex (LCR), a protective mechanism, causes closure of the glottis, coughing, and apnea during aspiration of the fluid into larynx/trachea and, therefore, has also postulated as one of the causes of SIDS (56, 57). On the other hand, DR, a subtype of TCR, has also been implicated to have a role in SIDS (14, 15, 58). The TCR is regulated by many brainstem nuclei and endogenously modulated by many neurotransmitters, the important one being serotonergic (5-HT), cholinergic (ACh), and nicotinergic (42, 59). Abnormalities in the modulation of these neurotransmitters along with defect in brainstem nuclei maturation may lead to exaggerated TCR response. Therefore, we summarize pieces of evidence in four hypotheses.

Serotonergic Hypothesis

Abnormalities of serotonergic neurons have been observed in victims of SIDS (60–67). These victims had a higher number of 5-HT neurons in the medulla and cerebrospinal fluid (68, 69). Also, these medullary 5-HT neurons have been proposed to act as central respiratory chemoreceptors that are involved in the facilitation of respiration in response to hypoxic episode and generation of respiratory rhythm (70–73). These observations suggest that medullary 5-HT dysfunction may result in loss of respiratory and autonomic response to hypoxia and hypercarbia leading to sudden death in SIDS victims during sleep. Interestingly, the 5-HT1A-binding density was more reduced in males compared to females' SIDS victims, which also explains why males are more vulnerable to SIDS (68, 74). Notably, these conditions (hypoxia, hypercarbia, and male gender) are also common risk factors for inciting the TCR. In animal experiment models, investigators have shown that the serotonin modulation is linked with TCR mechanism that further explains the possible role of TCR in SIDS (42, 75).

Cholinergic Hypothesis

The decrease in cholinergic receptors density, as well as binding dysfunction of cholinergic receptors, has also been implicated as a risk factor for SIDS. Investigators have found a reduction in some choline acetyltransferase (ChAT) neurons as well as their binding capacities in hypoglossal nucleus and dorsal motor nucleus of vagus in SIDS cases (76–84). Also, hypoplasia of the arcuate nucleus has also been observed in these infants (76, 85, 86). These findings suggest a specific defect in cholinergic neurons in the brainstem of SIDS infants, which could cause abnormal control of cardiovascular and respiratory functions in these babies and contribute to the etiology of SIDS (76). They observed that cholinergic neurons endogenously inhibit the excitatory glutamatergic transmission to parasympathetic cardiac vagal neurons in response to trigeminal nerve stimulation *via* mAChRs. Neostigmine (an acetylcholinesterase inhibitor) significantly inhibited, whereas atropine (muscarinic receptor antagonist) enhanced this transmission, thus demonstrating the role of muscarinic (m4 type mACh) receptors. A decreased cholinergic activity could result in reduced inhibition of excitatory neurotransmission to cardiac vagal neurons in response to trigeminal nerve stimulation and thus an exaggerated TCR response in SIDS infants (59). Cholinergic receptors also play a significant role in sleep-dependent changes. The cholinergic neurotransmission in the brainstem is an important integral component of rapid eyeball movement sleep generation (87, 88). Change in cholinergic receptor activity is associated with potentiation of TCR and trigeminally evoked respiratory suppression (89) as well as with altered sleep–awake cycles in infants both of which are also seen in victims of SIDS. Studies have identified incomplete and less frequent arousal from sleep in response to hypoxia in SIDS victims. Kato et al. studied the characteristics of arousal from sleep in 16 infants who were being monitored for some days or weeks before they died of SIDS. The polygraphic sleep recordings of these infants were compared with those of matched control infants. The result of this study showed significantly fewer cortical arousal (complete arousal) in an infant who eventually died of SIDS later than in the control infants. Victims of SIDS had more frequent and longer duration of subcortical arousal (incomplete arousal) than controls. This study suggested an incomplete arousal process from sleep in infants who succumb to SIDS (90). Sensory stimulation of the trigeminal nerve during REM sleep has been shown to cause REM sleep-associated respiratory failures in SIDS infants (89, 91).

Nicotine Hypothesis (Mixed Model)

Prenatal exposure of the fetus to nicotine alters the density and binding capacity of serotonin and cholinergic receptors (61, 63, 68, 80, 81, 92, 93) and is one of the major risk factors contributing to SIDS (94, 95). Gorini et al. used a rat model to study the effects of prenatal nicotine exposure in the offsprings of the mothers who were exposed to clinically significant nicotine levels during gestation (75). The results of this study showed an exaggerated TCR response in animals exposed to nicotine during the prenatal period. They observed that prenatal exposure to nicotine significantly facilitates excitatory glutamatergic neurotransmission to cardiac vagal neurons in the nucleus ambiguus upon stimulation of trigeminal sensory afferents compared to their unexposed counterparts. The prenatal nicotine exposure

also enhanced the endogenous serotonergic facilitation of TCR. All these effects thus lead to heightened TCR response (75). Also, a reduction in the number and function of AChRs has also been found in infants exposed to prenatal nicotine. Fetal exposure to nicotine suppresses mRNA expression and thus decreases brainstem mAChR binding. This again contributes to exaggeration of TCR by reduced inhibition of cardiac vagal neurons. Exposure to nicotine during the prenatal period facilitates modulation of inhibitory and excitatory pathways to the vagal nucleus in response to hypoxia or hypercapnia (96, 97). Prenatal exposure to nicotine decreases inhibitory GABAergic signals to the vagal nucleus during hypoxia (98) as well as hypercapnia (99). This decreased inhibitory GABAergic inputs to vagal nucleus cause increase in vagal activity to heart, thereby causing severe and sometimes lethal bradycardia in these animals (100–102). These findings suggest the likely cellular mechanism that causes an exaggerated response and pronounced bradycardia in victims of SIDS. Fetal exposure to nicotine also causes dysfunction of brainstem monoaminergic pathway. It leads to downregulation of 5-HT receptors and enhancing the risk of death due to SIDS (85). Prenatal nicotine exposure modulates 5-HT receptors in areas of brainstem regulating cardiorespiratory function that results in exaggerated TCR response and lethal outcome (75, 103).

Other Hypotheses

Frequent developmental abnormalities in the brain stem, particularly in the arcuate nucleus, have been identified in SIDS (85, 86, 104–106). The arcuate nucleus is an important cardiorespiratory center in the medulla and hypoplasia of this nucleus has been detected in over 50% of infants dying of SIDS (105). Alterations in another brainstem nucleus have also been demonstrated (85, 107–112). Some of these nuclei (e.g., nucleus ambiguus, parabrachial nucleus) also participate in the reflex arc of TCR (40, 42). Besides, Lavezzi et al. observed an association between tobacco use and decreased in the functional activity of trigeminal nucleus that can trigger sudden death in babies (108). On the other hand, SIDS may occur due to a lack of sufficient development and plasticity of glutamatergic synapses (insufficient glutamate signaling) in the mesencephalic nucleus of the trigeminal nerve and reticular formation of the brainstem (113). All these findings thus suggest the role of developmental defects (i.e., neuronal deficiency and immaturity) in the brainstem nuclei regulating cardiorespiratory and other autonomic function in infants who die of SIDS. Therefore, the TCR may be a missing link in the etiopathogenesis of this subgroup of patients as well.

CONCLUSION

Serotonergic or/and cholinergic dysfunction in the brainstem autonomic nuclei causes an exaggerated TCR response and thus culminates in sudden intense bradycardia, apnea, and death and, therefore, can be linked with the etiopathogenesis of SIDS. However, whether the exaggerated TCR response is the cause in all cases of SIDS is a subject for future research.

AUTHOR CONTRIBUTIONS

TC made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data, and helped in writing the manuscript. GS participated in drafting and writing the article. BB participated in writing the article. BS participated in writing and gave final approval of the version. All the authors have given final approval for submission of this version.

REFERENCES

1. Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. *Pediatr Pathol* (1991) 11:677–84. doi:10.3109/15513819109065465
2. Moon RY, Horne RS, Hauck FR. Sudden infant death syndrome. *Lancet* (2007) 370:1578–87. doi:10.1016/S0140-6736(07)61662-6
3. Hoyert DL. Mortality associated with birth defects: influence of successive disease classification revisions. *Birth Defects Res A Clin Mol Teratol* (2003) 67:651–5. doi:10.1002/bdra.10117
4. Misurya VK, Singh SP, Kulshrestha VK. Prevention of oculocardiac reflex (O.C.R) during extraocular muscle surgery. *Indian J Ophthalmol* (1990) 38:85–7.
5. Gilani SM, Jamil M, Akbar F, Jehangir R. Anticholinergic premedication for prevention of oculocardiac reflex during squint surgery. *J Ayub Med Coll Abbottabad* (2005) 17:57–9.
6. Hunsley JE, Bush GH, Jones CJ. A study of glycopyrrolate and atropine in suppression of oculocardiac reflex during strabismus surgery in children. *Br J Anaesth* (1982) 54:459–64. doi:10.1093/bja/54.4.459
7. Karhunen U, Cozanitis DA, Brander P. The oculocardiac reflex in adults. A dose response study of glycopyrrolate and atropine. *Anaesthesia* (1984) 39:524. doi:10.1111/j.1365-2044.1984.tb07354.x
8. Schaller B. Ketamine and decrease of oculocardiac reflex. *Acta Anesth Scand* (2008) 52:446. doi:10.1111/j.1399-6576.2007.01513.x
9. Gandevia SC, McCloskey DI, Potter EK. Reflex bradycardia occurring in response to diving, nasopharyngeal stimulation and ocular pressure, and its modification by respiration and swallowing. *J Physiol* (1978) 276:383–94. doi:10.1113/jphysiol.1978.sp012241
10. Horne RS, Parslow PM, Ferens D, Bandopadhayay P, Osborne A, Watts AM, et al. Arousal responses and risk factors for sudden infant death syndrome. *Sleep Med* (2002) 2:61–5. doi:10.1016/S1389-9457(02)00168-5
11. Horne RS, Parslow PM, Harding R. Respiratory control and arousal in sleeping infants. *Pediatr Respir Rev* (2004) 3:190–8. doi:10.1016/j.prrv.2004.04.011
12. Meny RG, Carroll JL, Carbone MT, Kelly DH. Cardiorespiratory recordings from infants dying suddenly and unexpectedly at home. *Pediatrics* (1994) 93:44–9.
13. Poets CF, Meny RG, Chobanian MR, Bonofiglo RE. Gasping and other cardiorespiratory patterns during sudden infant deaths. *Pediatr Res* (1999) 45:350–4. doi:10.1203/00006450-199903000-00010
14. Lobban CD. The human dive reflex as a primary cause of SIDS. A review of the literature. *Med J Aust* (1991) 155:561–3.
15. Lobban CD. The oxygen-conserving dive reflex re-examined as the principal contributory factor in sudden infant death. *Med Hypotheses* (1995) 44:273–7. doi:10.1016/0306-9877(95)90179-5
16. Lemaitre F, Chowdhury T, Schaller B. The trigeminocardiac reflex – a comparison with the diving reflex in humans. *Arch Med Sci* (2015) 11(2):419–26. doi:10.5114/aoms.2015.50974
17. Chowdhury T, Mendelowitz D, Golanov E, Spiriev T, Arasho B, Sandu N, et al. Trigeminocardiac reflex: the current clinical and physiological

knowledge. *J Neurosurg Anesthesiol* (2015) 27(2):136–47. doi:10.1097/ANA.0000000000000065
18. Schaller B, Cornelius JF, Sandu N, Ottaviani G, Perez-Pinzon MA. Oxygen-conserving reflexes of the brain: the current molecular knowledge. *J Cell Mol Med* (2009) 13(4):644–7. doi:10.1111/j.1582-4934.2009.00659.x
19. Chowdhury T, Schaller B. *Trigeminocardiac Reflex*. San Diego: Elsevier (2015).
20. Meuwly C, Golanov E, Chowdhury T, Erne P, Schaller B. Trigeminal cardiac reflex: new thinking model about the definition based on a literature review. *Medicine* (2015) 94:1–9. doi:10.1097/MD.0000000000000484
21. Sandu N, Chowdhury T, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). How to apply case reports in clinical practice using surrogate models via example of the trigeminocardiac reflex. *J Med Case Rep* (2016) 6(10):8. doi:10.1186/s13256-016-0849-z
22. Arasho B, Sandu N, Spiriev T, Prabhakar H, Schaller B. Management of the trigeminocardiac reflex: facts and own experience. *Neurol India* (2009) 57(4):375–80. doi:10.4103/0028-3886.55577
23. Sandu N, Sadr-Eshkevari P, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). Usefulness of case reports to improve medical knowledge regarding trigemino-cardiac reflex in skull base surgery. *J Med Case Rep* (2011) 15(5):149. doi:10.1186/1752-1947-5-149
24. Sandu N, Schaller B. The trigemino-cardiac reflex: a view to the future. *Arch Med Sci* (2010) 6(1):138–9. doi:10.5114/aoms.2010.13523
25. Schaller B, Filis A, Sandu N, Buchfelder M. Peripheral trigemino-cardiac reflex. *Acta Neurochir (Wien)* (2009) 151(12):1727. doi:10.1007/s00701-009-0390-6
26. Schaller B, Filis A, Sandu N, Rasper J, Noethen C, Buchfelder M. Trigemino-cardiac reflex may be refractory to conventional management in adults. *Acta Neurochir (Wien)* (2008) 150(9):929–30. doi:10.1007/s00701-008-0010-x
27. Schaller BJ, Filis A, Buchfelder M. Trigemino-cardiac reflex in humans initiated by peripheral stimulation during neurosurgical skull-base operations. Its first description. *Acta Neurochir (Wien)* (2008) 150(7):715–7. doi:10.1007/s00701-008-1602-1
28. Schaller BJ, Filis A, Buchfelder M. Detection and prevention of the trigeminocardiac reflex during skull base surgery. *Acta Neurochir (Wien)* (2007) 149(3):331. doi:10.1007/s00701-006-1088-7
29. Schaller BJ. Trigeminocardiac reflex. *J Neurosurg* (2007) 107(1):243. doi:10.3171/JNS-07/07/0243
30. Spiriev T, Sandu N, Kondoff S, Tzekov C, Schaller B. Tic and autonomic symptoms. *J Neurosurg* (2012) 116(6):1397–8. doi:10.3171/2011.9.JNS111532
31. Chowdhury T, Sandu N, Sadr-Eshkevari P, Meuwly C, Schaller B. Trigeminocardiac reflex: current trends. *Expert Rev Cardiovasc Ther* (2014) 12(1):9–11. doi:10.1586/14779072.2014.862498
32. Schaller BJ, Sandu N, Cornelius JF, Filis A, Perez-Pinzon MA. Oxygen-conserving implications of the trigemino-cardiac reflex in the brain: the molecular basis of neuroprotection? *Mol Med* (2009) 15(5–6):125–6. doi:10.2119/molmed.2009.00013
33. Spiriev T, Tzekov C, Laleva L, Kostadinova C, Kondoff S, Sandu N, et al. Central trigeminocardiac reflex in pediatric neurosurgery: a case report and review of the literature. *J Med Case Rep* (2012) 6:372. doi:10.1186/1752-1947-6-372
34. Schaller BJ, Buchfelder M. Trigemino-cardiac reflex in skull base surgery: from a better understanding to a better outcome? *Acta Neurochir (Wien)* (2006) 148(10):1029–31. doi:10.1007/s00701-006-0889-z
35. Schaller B, Cornelius JF, Prabhakar H, Koerbel A, Gnanalingham K, Sandu N, et al. The trigeminocardiac reflex: an update of the current knowledge. *J Neurosurg Anesthesiol* (2009) 21:187–95. doi:10.1097/ANA.0b013e3181a2bf22
36. Ohshita N, Nakajo N, Takemura M. Characteristics of the trigeminal depressor response in cats. *J Neurosci Res* (2004) 76:891–901. doi:10.1002/jnr.20131
37. McCulloch PF, Faber KM, Panneton WM. Electrical stimulation of the anterior ethmoidal nerve produces the diving response. *Brain Res* (1999) 830:24–31. doi:10.1016/S0006-8993(99)01374-8
38. Nalivaiko E, De Pasquale CG, Blessing WW. Electrocardiographic changes associated with the nasopharyngeal reflex in conscious rabbits: vago-sympathetic co-activation. *Auton Neurosci* (2003) 105:101–4. doi:10.1016/S1566-0702(03)00048-1
39. Chowdhury T, Sandu N, Meuwly C, Cappellani RB, Schaller B. Trigeminocardiac reflex: differential behavior and risk factors around the course of the trigeminal nerve. *Future Neurol* (2014) 9:41–7. doi:10.2217/fnl.13.62
40. Schaller B. Trigeminocardiac reflex: a clinical phenomenon or a new physiological entity. *Neurology* (2004) 251:658–65. doi:10.1007/s00415-004-0458-4
41. Cornelius JF, Sadr-Eshkevari P, Arasho BD, Sandu N, Spiriev T, Lemaitre F, et al. The trigemino-cardiac reflex in adults: own experience. *Expert Rev Cardiovasc Ther* (2010) 8:895–8. doi:10.1586/erc.10.74
42. Gorini C, Jameson HS, Mendelowitz D. Serotonergic modulation of the trigeminocardiac reflex neurotransmission to cardiac vagal neurons in the nucleus ambiguus. *J Neurophysiol* (2009) 102:1443–50. doi:10.1152/jn.00287.2009
43. Alboni P, Alboni M, Gianfranchi L. Diving bradycardia: a mechanism of defence against hypoxic damage. *J Cardiovasc Med (Hagerstown)* (2011) 12:422–7. doi:10.2459/JCM.0b013e328344bcdc
44. Sandu N, Cornelius J, Filis A, Nöthen C, Rasper J, Kulinsky VI, et al. Cerebral hemodynamic changes during the trigeminocardiac reflex: description of a new animal model protocol. *ScientificWorldJournal* (2010) 10:1416–23. doi:10.1100/tsw.2010.136
45. Sandu N, Spiriev T, Lemaitre F, Filis A, Schaller B. New molecular knowledge towards the trigemino-cardiac reflex as a cerebral oxygen-conserving reflex. *ScientificWorldJournal* (2010) 4(10):811–7. doi:10.1100/tsw.2010.71
46. Goksor E, Rosengren L, Wennergren G. Bradycardic response during submersion in infant swimming. *Acta Paediatr* (2002) 91:307–12. doi:10.1111/j.1651-2227.2002.tb01720.x
47. Foster GE, Sheel AW. The human diving response, its function, and its control. *Scand J Med Sci Sports* (2005) 15:3–12. doi:10.1111/j.1600-0838.2005.00440.x
48. Gooden BA. Mechanism of the human diving response. *Integr Physiol Behav Sci* (1994) 29(1):6–16. doi:10.1007/BF02691277
49. Liner MH. Tissue gas stores of the body and head-out immersion in humans. *J Appl Physiol* (1993) 75(3):1285–93.
50. Matturri L, Ottaviani G, Lavezzi AM. Sudden infant death triggered by dive reflex. *J Clin Pathol* (2005) 58:77–80. doi:10.1136/jcp.2004.020867
51. Fewell JE, Smith FG, Ng VK. Prenatal exposure to nicotine impairs protective responses of rat pups to hypoxia in an age-dependent manner. *Respir Physiol* (2001) 127:61–73. doi:10.1016/S0034-5687(01)00232-8
52. Nachmanoff DB, Panigrahy A, Filiano JJ, Mandell F, Sleeper LA, Valdes-Dapena M, et al. Brainstem 3H-nicotine receptor binding in the sudden infant death syndrome. *J Neuropathol Exp Neurol* (1998) 57:1018–25. doi:10.1097/00005072-199811000-00004
53. Ramet J, Praud JP, D'Allest AM, Dehan M, Gaultier C. Trigeminal airstream stimulation. Maturation-related cardiac and respiratory responses during REM sleep in human infants. *Chest* (1990) 98(1):92–6.
54. Cote A, Hum C, Brouillette RT, Themens M. Frequency and timing of recurrent events in infants using home cardiorespiratory monitors. *J Pediatr* (1998) 132:783–9. doi:10.1016/S0022-3476(98)70304-X
55. Jones KL, Krous HF, Nadeau J, Blackbourne B, Zielke HR, Gozal D. Vascular endothelial growth factor in the cerebrospinal fluid of infants who died of sudden infant death syndrome: evidence for antecedent hypoxia. *Pediatrics* (2003) 111:358–63. doi:10.1542/peds.111.2.358
56. Thach BT. Maturation and transformation of reflexes that protect the laryngeal airway from liquid aspiration from fetal to adult life. *Am J Med* (2003) 111(Suppl 8A):69S–77S. doi:10.1016/S0002-9343(01)00860-9
57. Leiter JC, Böhm I. Mechanisms of pathogenesis in the sudden infant death syndrome. *Respir Physiol Neurobiol* (2007) 159(2):127–38. doi:10.1016/j.resp.2007.05.014
58. Morpurgo CV, Lavezzi AM, Ottaviani G, Rossi L. Bulbo-spinal pathology and sudden respiratory infant death syndrome. *Eur J Anaesthesiol* (2004) 21:589–93. doi:10.1097/00003643-200408000-00001
59. Gorini C, Philbin K, Bateman R, Mendelowitz D. Endogenous inhibition of the trigeminally evoked neurotransmission to cardiac vagal neurons by muscarinic acetylcholine receptors. *J Neurophysiol* (2010) 104:1841–8. doi:10.1152/jn.00442.2010
60. Kinney HC, Randall LL, Sleeper LA, Willinger M, Belliveau RA, Zec N, et al. Serotonergic brainstem abnormalities in Northern Plains Indians with the sudden infant death syndrome. *J Neuropathol Exp Neurol* (2003) 62:1178–91. doi:10.1093/jnen/62.11.1178
61. Panigrahy A, Filiano J, Sleeper LA, Mandell F, Valdes-Dapena M, Krous HF, et al. Decreased serotonergic receptor binding in rhombic lip-derived regions

of the medulla oblongata in the sudden infant death syndrome. *J Neuropathol Exp Neurol* (2000) 59:377–84. doi:10.1093/jnen/59.5.377
62. Kinney HC, Myers MM, Belliveau RA, Randall LL, Trachtenberg FL, Fingers ST, et al. Subtle autonomic and respiratory dysfunction in sudden infant death syndrome associated with serotonergic brainstem abnormalities: a case report. *J Neuropathol Exp Neurol* (2005) 64:689–94. doi:10.1097/01.jnen.0000174334.27708.43
63. Hunt CE. Gene-environment interactions: implications for sudden unexpected deaths in infancy. *Arch Dis Child* (2005) 90:48–53. doi:10.1136/adc.2004.051458
64. Narita N, Narita M, Takashima S, Nakayama M, Nagai T, Okado N. Serotonin transporter gene variation is a risk factor for sudden infant death syndrome in the Japanese population. *Pediatrics* (2001) 107:690–2. doi:10.1542/peds.107.4.690
65. Weese-Mayer DE, Berry-Kravis EM, Maher BS, Silvestri JM, Curran ME, Marazita ML. Sudden infant death syndrome: association with a promoter polymorphism of the serotonin transporter gene. *Am J Med Genet* (2003) 117:268–74. doi:10.1002/ajmg.a.20005
66. Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML. Association of the serotonin transporter gene with sudden infant death syndrome: a haplotype analysis. *Am J Med Genet* (2003) 122:238–45. doi:10.1002/ajmg.a.20427
67. Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Curran ME, Silvestri JM, et al. Sudden infant death syndrome: case-control frequency differences at genes pertinent to early autonomic nervous system embryologic development. *Pediatr Res* (2004) 56:391–6. doi:10.1203/01.PDR.0000136285.91048.4A
68. Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, et al. Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *JAMA* (2006) 296:2124–32. doi:10.1001/jama.296.17.2124
69. Caroff J, Girin E, Alix D, Cann-Moisan C, Sizun J, Barthelemy L. Neurotransmission and sudden infant death. Study of cerebrospinal fluid. *CR Acad Sci III* (1992) 314:451–4.
70. Richerson GB. Serotonergic neurons as carbon dioxide sensors that maintain pH homeostasis. *Nat Rev Neurosci* (2004) 5:449–61. doi:10.1038/nrn1409
71. Messier ML, Li A, Nattie EE. Inhibition of medullary raphe serotonergic neurons has age-dependent effects on the CO_2 response in newborn piglets. *J Appl Physiol* (2004) 96:1909–19. doi:10.1152/japplphysiol.00805.2003
72. Baker-Herman TL, Fuller DD, Bavis RW, Zabka AG, Golder FJ, Doperalski NJ, et al. BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. *Nat Neurosci* (2004) 7:48–55. doi:10.1038/nn1166
73. Pena F, Ramirez JM. Endogenous activation of serotonin-2A receptors is required for respiratory rhythm generation in vitro. *J Neurosci* (2002) 22:11055–64.
74. American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. The changing concept of sudden infant death syndrome: diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. *Pediatrics* (2005) 116:1245–55. doi:10.1542/peds.2005-1499
75. Gorini C, Jameson H, Woerman AL, Perry DC, Mendelowitz D. Prenatal nicotine exposure enhances the trigeminocardiac reflex via serotonin receptor facilitation in brainstem pathways. *J Appl Physiol* (2013) 115:415–21. doi:10.1152/japplphysiol.00552.2013
76. Mallard C, Tolcos M, Leditschke J, Campbell P, Rees S. Reduction in choline acetyltransferase immunoreactivity but not muscarinic-m2 receptor immunoreactivity in the brainstem of SIDS infants. *J Neuropathol Exp Neurol* (1999) 58:255–64. doi:10.1097/00005072-199903000-00005
77. Kalaria RN, Fiedler C, Hunsaker JC III, Sparks DL. Synaptic neurochemistry of human striatum during development: changes in sudden infant death syndrome. *J Neurochem* (1993) 60:2098–105. doi:10.1111/j.1471-4159.1993.tb03494.x
78. Sparks DL, Hunsaker JC III. Sudden infant death syndrome: altered aminergic-cholinergic synaptic markers in hypothalamus. *J Child Neurol* (1991) 6:335–9. doi:10.1177/088307389100600409
79. Oda Y. Choline acetyltransferase: the structure, distribution and pathologic changes in the central nervous system. *Pathol Int* (1999) 49:921–37. doi:10.1046/j.1440-1827.1999.00977.x
80. Kinney HC. Brainstem mechanisms underlying the sudden infant death syndrome: evidence from human pathologic studies. *Dev Psychobiol* (2009) 51:223–33. doi:10.1002/dev.20367
81. Kinney HC, Filiano JJ, Sleeper LA, Mandell F, Valdes-Dapena M, White WF. Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. *Science* (1995) 269:1446–50. doi:10.1126/science.7660131
82. Slotkin TA, Epps TA, Stenger ML, Sawyer KJ, Seidler FJ. Cholinergic receptors in heart and brainstem of rats exposed to nicotine during development: implications for hypoxia tolerance and perinatal mortality. *Brain Res Dev Brain Res* (1999) 113:1–12. doi:10.1016/S0165-3806(98)00173-4
83. Zhu J, Taniguchi T, Konishi Y, Mayumi M, Muramatsu I. Nicotine administration decreases the number of binding sites and mRNA of M1 and M2 muscarinic receptors in specific brain regions of rat neonates. *Life Sci* (1998) 62:1089–98.
84. Kubo S, Orihara Y, Gotohda T, Tokunaga I, Tsuda R, Ikematsu K, et al. Immunohistochemical studies on neuronal changes in brain stem nucleus of forensic autopsied cases. II. Sudden infant death syndrome. *Nihon Hoigaku Zasshi* (1998) 52:350–4.
85. Matturri L, Ottaviani G, Alfonsi G, Crippa M, Rossi L, Lavezzi AM. Study of the brainstem, particularly the arcuate nucleus, in sudden infant death syndrome (SIDS) and sudden intra-uterine unexplained death (SIUD). *Am J Forensic Med Pathol* (2004) 25:44–8. doi:10.1097/01.paf.0000113813.83779.21
86. Filiano JJ, Kinney HC. Arcuate nucleus hypoplasia in the sudden infant death syndrome. *J Neuropathol Exp Neurol* (1992) 51:394–403. doi:10.1097/00005072-199207000-00002
87. Vazquez J, Baghdoyan HA. GABAA receptors inhibit acetylcholine release in cat pontine reticular formation: implications for REM sleep regulation. *J Neurophysiol* (2004) 92:2198–206. doi:10.1152/jn.00099.2004
88. Verret L, Leger L, Fort P, Luppi PH. Cholinergic and noncholinergic brainstem neurons expressing Fos after paradoxical (REM) sleep deprivation and recovery. *Eur J Neurosci* (2005) 21:2488–504. doi:10.1111/j.1460-9568.2005.04060.x
89. Dutschmann M, Herbert H. Pontine cholinergic mechanisms enhance trigeminally evoked respiratory suppression in the anesthetized rat. *J Appl Physiol* (1999) 87:1059–65.
90. Kato I, Franco P, Groswasser J, Scaillet S, Kelmanson I, Togari H, et al. Incomplete arousal processes in infants who were victims of sudden death. *Am J Respir Crit Care Med* (2003) 168:1298–303. doi:10.1164/rccm.200301-134OC
91. Gould JB, Lee AF, Morelock S. The relationship between sleep and sudden infant death. *Ann N Y Acad Sci* (1988) 533:62–77. doi:10.1111/j.1749-6632.1988.tb37234.x
92. Hunt CE, Hauck FR. Sudden infant death syndrome. *CMAJ* (2006) 174:1861–9. doi:10.1503/cmaj.051671
93. Frank MG, Srere H, Ledezma C, O'Hara B, Heller HC. Prenatal nicotine alters vigilance states and AChR gene expression in the neonatal rat: implications for SIDS. *Am J Physiol Regul Integr Comp Physiol* (2001) 280:R1134–40.
94. Duncan JR, Garland M, Myers MM, Fifer WP, Yang M, Kinney HC, et al. Prenatal nicotine-exposure alters fetal autonomic activity and medullary neurotransmitter receptors: implications for sudden infant death syndrome. *J Appl Physiol* (2009) 107:1579–90. doi:10.1152/japplphysiol.91629.2008
95. Slotkin TA, Seidler FJ. Mimicking maternal smoking and pharmacotherapy of preterm labor: fetal nicotine exposure enhances the effect of late gestational dexamethasone treatment on noradrenergic circuits. *Brain Res Bull* (2011) 86:435–40. doi:10.1016/j.brainresbull.2011.08.009
96. Huang ZG, Griffioen KJ, Wang X, Dergacheva O, Kamendi H, Gorini C, et al. Nicotinic receptor activation occludes purinergic control of central cardiorespiratory network responses to hypoxia/hypercapnia. *J Neurophysiol* (2007) 98:2429–38. doi:10.1152/jn.00448.2007
97. Kamendi H, Stephens C, Dergacheva O, Wang X, Huang ZG, Bouairi E, et al. Prenatal nicotine exposure alters the nicotinic receptor subtypes that modulate excitation of parasympathetic cardiac neurons in the nucleus ambiguus from primarily alpha3beta2 and/or alpha6betaX to alpha3beta4. *Neuropharmacology* (2006) 51:60–6. doi:10.1016/j.neuropharm.2006.03.001
98. Neff RA, Simmens SJ, Evans C, Mendelowitz D. Prenatal nicotine exposure alters central cardiorespiratory responses to hypoxia in rats: implications for sudden infant death syndrome. *J Neurosci* (2004) 24:9261–8. doi:10.1523/JNEUROSCI.1918-04.2004

99. Huang ZG, Griffioen KJ, Wang X, Dergacheva O, Kamendi H, Gorini C, et al. Differential control of central cardiorespiratory interactions by hypercapnia and the effect of prenatal nicotine. *J Neurosci* (2006) 26:21–9. doi:10.1523/JNEUROSCI.4221-05.2006
100. Huang ZG, Wang X, Evans C, Gold A, Bouairi E, Mendelowitz D. Prenatal nicotine exposure alters the types of nicotinic receptors that facilitate excitatory inputs to cardiac vagal neurons. *J Neurophysiol* (2004) 92:2548–54. doi:10.1152/jn.00500.2004
101. Huang ZG, Wang X, Dergacheva O, Mendelowitz D. Prenatal nicotine exposure recruits an excitatory pathway to brainstem parasympathetic cardioinhibitory neurons during hypoxia/hypercapnia in the rat: implications for sudden infant death syndrome. *Pediatr Res* (2005) 58:562–7. doi:10.1203/01.PDR.0000179380.41355.FC
102. Evans C, Wang J, Neff R, Mendelowitz D. Hypoxia recruits a respiratory-related excitatory pathway to brainstem premotor cardiac vagal neurons in animals exposed to prenatal nicotine. *Neuroscience* (2005) 133:1073–9. doi:10.1016/j.neuroscience.2005.03.053
103. Slotkin TA, Seidler FJ. Mimicking maternal smoking and pharmacotherapy of preterm labor: interactions of fetal nicotine and dexamethasone on serotonin and dopamine synaptic function in adolescence and adulthood. *Brain Res Bull* (2010) 82:124–34. doi:10.1016/j.brainresbull.2010.02.015
104. Matturri L, Biondo B, Mercurio P, Rossi L. Severe hypoplasia of medullary arcuate nucleus: quantitative analysis in sudden infant death syndrome. *Acta Neuropathol* (2000) 99:371–5. doi:10.1007/s004010051138
105. Matturri L, Biondo B, Suarez-Mier MP, Rossi L. Brainstem lesions in the sudden infant death syndrome: variability in the hypoplasia of the arcuate nucleus. *Acta Neuropathol* (2002) 104:12–20. doi:10.1007/s00401-001-0511-7
106. Lavezzi AM, Ottaviani G, Mauri M, Matturri L. Hypoplasia of the arcuate nucleus and maternal smoking during pregnancy in sudden unexplained perinatal and infant death. *Neuropathology* (2004) 24:284–9. doi:10.1111/j.1440-1789.2004.00558.x
107. Ottaviani G, Matturri L, Mingrone R, Lavezzi AM. Hypoplasia and neuronal immaturity of the hypoglossal nucleus in sudden infant death. *J Clin Pathol* (2006) 59:497–500. doi:10.1136/jcp.2005.032037
108. Lavezzi AM, Mehboob R, Matturri L. Developmental alterations of the spinal trigeminal nucleus disclosed by substance P immunohistochemistry in fetal and infant sudden unexplained deaths. *Neuropathology* (2011) 31:405–13. doi:10.1111/j.1440-1789.2010.01190.x
109. Lavezzi AM, Ottaviani G, Mingrone R, Matturri L. Analysis of the human locus coeruleus in perinatal and infant sudden unexplained deaths. Possible role of the cigarette smoking in the development of this nucleus. *Brain Res Dev Brain Res* (2005) 154:71–80. doi:10.1016/j.devbrainres.2004.10.007
110. Matturri L, Ottaviani G, Lavezzi AM. Techniques and criteria in pathologic and forensic-medical diagnostics of sudden unexpected infant and perinatal death. *Am J Clin Pathol* (2005) 124:259–68. doi:10.1309/J6AR-EY41-HKBE-YVHX
111. Matturri L, Ottaviani G, Benedetti G, Agosta E, Lavezzi AM. Unexpected perinatal death and sudden infant death syndrome (SIDS): anatomopathological and legal aspects. *Am J Forensic Med Pathol* (2005) 26:155–60.
112. Lavezzi AM, Ottaviani G, Rossi L, Matturri L. Hypoplasia of the parabrachial/Kölliker-fuse complex in perinatal death. *Biol Neonate* (2004) 86:92–7. doi:10.1159/000078310
113. Andrisani G, Andrisani G. The mesencephalic nucleus of the trigeminal nerve and the SIDS. *Med Hypotheses* (2015) 84(1):8–10. doi:10.1016/j.mehy.2014.11.005

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frontiers in Neurology

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The Role of Acute Trigemino-Cardiac Reflex in Unusual, Non-Surgical Cases: A Review

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Trigemino-cardiac reflex (TCR) is a well-established phenomenon that is mainly reported in the various surgical specialties. However, the role of this unique reflex is entirely unknown in other medicine domains. Therefore, the present mini-review aims to explore the role of TCR in such unusual cases and also highlights the importance of case reports for knowledge creation in such context.

Keywords: trigemino-cardiac reflex, asystole, death, brainstem reflex

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INTRODUCTION

In the last 20 years, there has been a substantial interest among the neuroscientists about the unique brainstem reflex, known as "trigemino-cardiac reflex" (TCR). This reflex is usually incited by the stimulation of the fifth nerve along its entire course, anywhere from the peripheral division to the central connections (1–5). Interestingly, the occurrence of the TCR episodes is not only limited to neurosurgical procedures/interventions but also explored and reported in various other non-neurosurgical procedures including ocular surgeries, oral–facial–maxillary surgeries, dental procedures, dermatological surgeries, etc. (1–12). In general, irrespective of the nature of the surgery, the common manifestation of the TCR remains almost similar that include bradycardia, hypotension, apnea, and/or gastric hypermotility. In addition to the usual association of the TCR to various surgical procedures in the vicinity of the trigeminal nerve, there are only very few reports that do highlight the unusual as well as the catastrophic nature of the TCR in non-surgical conditions, and further expands the knowledge and understanding of TCR in other domains of medicine. Such reports underline the connection from the TCR to the dive reflex or sudden infant death syndrome. From the extensive surgical/interventional reports, however, one might assume that such non-surgical cases might be underreported. Therefore, the present mini-review aims to explore the role of TCR in such unusual cases and also highlights the importance of case reports for knowledge creation in such context.

METHOD

Definition of the TCR

The TCR is defined here as the sudden onset of parasympathetic dysrhythmia, hypotension, apnea, or gastric hypermotility during stimulation of any of the sensory branches of the trigeminal nerve. A TCR should include a decrease in heart rate (HR) and mean arterial blood pressure (MABP) of more than 20% as compared with baseline values before application of the stimulus and coincide with the surgical manipulation at or around any branches of the trigeminal nerve (7).

Review of Literature

We have searched terms including "trigemino-cardiac reflex," "trigeminal-cardiac reflex," "oculocardiac reflex (OCR)" in various search engines including PubMed, Google, EMBASE, and SCOPUS from January 1, 1970 to August 1, 2016. All cross references are also carefully reviewed.

Inclusion Criteria

Articles that clearly described TCR or OCR as a cause of hemodynamic/respiratory changes as defined above in any age group and either of the sexes in human subjects was included. All the papers irrespective of the type and language were also included in this review (**Table 1**). Episodes of TCR or OCR that were followed by surgery or other neuro-interventions were also included.

Exclusion Criteria

Patients with prior history of cardiac disease, b-blockers, other medications prone to cause bradycardia, and TCR or OCR episodes occurring during any surgical or interventional procedures were excluded. Chronic TCR appearance was excluded. Injury or inciting events that predisposed the TCR or the OCR episodes and reported in three or more than three papers were also excluded.

RESULTS

Out of all the screened papers, only four articles met the stringent inclusion and exclusion criteria (13–16). Out of these four, two cases (50%) report epistaxis and two (50%) forensic investigations (**Table 1**). All the four patients died because of cardiac arrest. Out of the four patients mentioned in these reports, three (75%) were male of 56–69 years of age and one (25%) was elderly (age not mentioned) female.

First two papers highlighted that epistaxis was a presenting symptom, and the nasal packing was done to control the nasal bleeding in both the patients (13, 14). After the nasal packing, the first patient (65/M) developed bradycardia, a decrease in oxygen saturation (50%), and hypotension after 15 min, whereas the second patient (69/M) first showed respiratory distress (oxygen saturation 76%) followed by bradycardia. Both the patients were managed by endotracheal intubation and advanced cardiac life support (ACLS). Unfortunately, both the patients could not be revived back and died. Strikingly, nasal packs were not removed during the resuscitation phase in both the patients. Other two papers reported the forensic involvement (15, 16). Here, the first forensic report, a 58-year-old male with a history of depression presented with a suicidal fire case. Interestingly, in the first instance, the external examination and other forensic evaluation reports directed the cause of death as one of the mechanisms related to burn; however, in the absence of obvious pathological findings of burn, subsequent internal examination, and toxicological analysis ruled out the usual mechanisms and postulated the neurogenic mechanism (TCR). The second case, a violent stabbing on the elderly female led to bilateral ocular injuries and multiple facial and neck injuries. Interestingly, at the first instance, it appeared that the cause of death was head and neck injuries. However, subsequent investigations revealed no obvious cause and thus suspected OCR (a peripheral TCR) as the cause of this demise.

TABLE 1 | Unusual cases of trigemino-cardiac reflex.

S. no.	Age/gender	Procedure	Hemodynamics	Outcome
1	65/M	Nasal packing	Bradycardia, apnea, hypotension	Died
2	69/M	Nasal packing	Dyspnea, bradycardia, pulseless electrical activity	Died
3	58/M	Suicidal fire	Cardiac arrest	Died
4	Elderly/F	Homicide	Cardiac arrest	Died

DISCUSSION

Trigemino-cardiac reflex is an interesting phenomenon that hitherto has primarily been focused on different surgical procedures including neurosurgical/neuro-interventions, dental, oral–facial–maxillary, and ocular surgeries in which upon the stimulation of the trigeminal nerve along its entire course predisposes the cardiorespiratory and gastric symptoms. These include negative chronotropic from mild (bradycardia) to severe (asystole) changes, bradypnea, apnea, and gastric hypermotility (1–12). Although the mechanism of the TCR is very complex but generally accepted mechanism includes that following the stimulation of the any sensory branch of the trigeminal nerve, signals are carried to the sensory nucleus of the trigeminal nerve *via* the Gasserian ganglion. This afferent pathway continues along the short internuncial nerve fibers in the reticular formation to connect with the efferent pathway in the motor nucleus of the vagus nerve. These terminate in the cardiac ganglia from which the postganglionic fibers are sent to the conductive system, leading to autonomic changes that usually manifest as a negative chronotropy (5, 17). So far, extensive investigations have been done to extract the role of TCR in various surgical procedures, neuro-interventions, different manifestations (cardiorespiratory changes), various definitions, and effect on outcome; however, the TCR in the majority of the reported literature seems a mild manifestation that is usually transient in nature (1–12).

Strikingly, after reviewing these above four papers, it seems clear that the TCR phenomenon is not merely limited to the surgical domain. Instead, it can have deleterious effects in other non-surgical specialties or procedures. The two cases of nasal packing induced severe cardiorespiratory disturbances clearly highlighted that the TCR episodes could result in fatal outcome. It worth to be mentioned that a fatal outcome is rarely described during surgery/intervention; if this is a publication bias or a characteristic phenomenon of the non-surgical cases. Notably, the nasal packs in both the cases were not removed during these events (13, 14). Whether or not, the outcome could have been different if these nasal packs would have been taken out is a matter of further research in animal models. However, as per the classical definition of the TCR, the removal of the nasal pack could have been aborted the TCR and related deleterious effect. These two cases certainly show the paramount importance of knowledge and recognition of TCR episodes in such a common scenario. On the other hand, the two other papers related to forensic pathology

did reveal the importance of this unique brain stem reflex for the scenarios in which there were lack substantial evidence or clues. In the homicidal fire case, the thermal stimulation on the face incited the TCR and thus patient sudden cardiac arrest (15). Similarly, in the second case, the penetrating injuries in eyes and orbits triggered the OCR, a peripheral subtype of TCR and resulted in the sudden death of the patient (16). Whether or not, sudden death in such cases (where forensic investigations, autopsy, and toxicological analysis do not reveal apparent cause) could be due to TCR/OCR is a matter of further research.

In all four cases, there was a clear cause-and-effect relationship. On the one side, this is evidence of a TCR, and the stimulation of the trigeminal root, on the other hand, this represents as well as confirms the afferent pathway of the TCR. If just one such observational case does not fit completely with the initial proposition, the hypothesis should be considered generally not valid and therefore should be revised or even rejected. This was not the case with our hypothesis of the existence of the TCR in non-surgical case reports and demonstrates that – besides the qualitative method of triangulation – the ongoing description of similar cases about a specific topic has importance not only for clinical practice but also for the scientific community (18, 19). However, after reviewing these non-surgical cases, the TCR phenomenon would certainly add the list of differential diagnoses in such situations. Also, this review also justifies that the case reports can also provide substantial knowledge and understanding of such phenomenon like the TCR. Our previous work also supports this notion that the case reports can have extraordinary significance for the elucidation of the rarer yet clinically relevant phenomenon, such as TCR.

Our work has some limitations. We have only found four cases, so that this case series does not impart the complete and more specific knowledge of TCR in such cases. However, the trend is so strong (hundreds of surgical cases without any fatal outcome and four of the four cases with fatal outcome) that we should think about an adaption of our previous model of the TCR. This is also the second principal limitation that we cannot yet explain this differential behavior in a meta-context.

In conclusion, this review shows that the existence of the TCR episodes can also occur in non-surgical as well as simple maneuvers and can lead to devastating complications including death. Therefore, this review further opens the understanding of the TCR phenomenon in various medicine domains as well.

AUTHOR CONTRIBUTIONS

TC helped in developing the concept, designing, data collection, data interpretation, and writing the manuscript. BS gave substantial inputs in developing the concept and writing the manuscript. Both the authors accepted the final version.

REFERENCES

1. Chowdhury T, Sandu N, Meuwly C, Cappellani RB, Schaller B. Trigeminal cardiac reflex: differential behavior and risk factors around the course of the trigeminal nerve. *Future Neurol* (2014) 9:41–7. doi:10.2217/fnl.13.62
2. Chowdhury T, Sandu N, Meuwly C, Schaller B. Trigeminal cardiac reflex: current trends. *Exp Rev Cardiovasc Ther* (2014) 12(1):9–11. doi:10.1586/14779072.2014.862498
3. Chowdhury T, Meuwly C, Sandu N, Schaller B, Cappellani RB. Coronary spasm in neurosurgical patients and role of trigemino-cardiac reflex: a review. *Neurol Res Int* (2014) 2014:5. doi:10.1155/2014/9749
4. Sandu N, Chowdhury T, Sadr-Eshkevari P, Filis A, Arasho B, Spiriev T, et al. Trigeminocardiac reflex during cerebellopontine angle surgery: anatomical location as a new risk factor. *Future Neurol* (2015) 10(1):7–13. doi:10.2217/fnl.14.66
5. Chowdhury T, Mendelowitz D, Govlanov E, Spiriev T, Belachew A, Sandu N, et al. Trigeminocardiac reflex: an update of the current clinical and physiological knowledge. *J Neurosurg Anesthesiol* (2015) 27(2):136–47. doi:10.1097/ANA.0000000000000065
6. Chowdhury T, Petropolis A, Cappellani RB. Cardiac emergencies in neurosurgical patients. *Bio Med Res Int* (2015) 2015:14. doi:10.1155/2015/751320
7. Meuwly C, Golanov E, Chowdhury T, Erne P, Schaller B. Trigemino cardiac reflex: new thinking model about the definition based on a literature review. *Medicine* (2015) 94(5):e484. doi:10.1097/MD.0000000000000484
8. Lemaitre F, Chowdhury T, Schaller B. The trigeminocardiac reflex – a comparison with the diving reflex in humans. *Arch Med Sci* (2015) 11(2):419–26. doi:10.5114/aoms.2015.50974
9. Meuwly C, Chowdhury T, Sandu N, Reck M, Erne P, Schaller B. Has anesthesia any influence on occurrence and treatment of the trigeminocardiac re-flex? A systematic review. *Medicine* (2015) 94(18):e807. doi:10.1097/MD.0000000000000807
10. Chowdhury T, Nöthen C, Filis A, Sandu N, Buchfelder M, Schaller B. Surgery for pituitary adenomas and intraoperative trigemino-cardiac reflex: first description of functional influence. *Medicine* (2015) 94(37):e1463. doi:10.1097/MD.0000000000001463
11. Chowdhury T, Cappellani RB, Schaller B. Chronic trigemino-cardiac reflex in patient with orbital floor fracture: role of surgery and first description. *J Neurosurg Anesthesiol* (2014) 26(1):91–2. doi:10.1097/ANA.0b013e3182a1a691
12. Chowdhury T, West M. Intraoperative asystole in a patient undergoing craniotomy under monitored anesthesia care: is it TCR? *J Neurosurg Anesthesiol* (2013) 25(1):92–3. doi:10.1097/ANA.0b013e318277d38a
13. Awasthi D, Roy TM, Byrd RP Jr. Epistaxis and death by the trigeminocardiac reflex: a cautionary report. *CCJM* (2015) 32(6):45–9.
14. Awasthi D, Byrd RP Jr, Roy TM. Fatal epistaxis: case report and review of the trigemino-cardiac reflex. *Prim Care Cardiovasc J.* doi:10.3132/pccj.2012.028
15. Rossi R, Lodise M, Lancia M, Bacci M, De-Giorgio F, Cascini F. Trigeminocardiac reflex as lethal mechanism in a suicidal fire death case. *J Forensic Sci* (2014) 59(3):833–5. doi:10.1111/1556-4029.12408
16. Lynch MJ, Parker H. Forensic aspects of ocular injury. *Am J Forensic Med Pathol* (2000) 21(2):124–6. doi:10.1097/00000433-200006000-00006
17. Cheng Z, Powley TL. Nucleus ambiguus projections to cardiac ganglia of rat atria: an anterograde tracing study. *J Comp Neurol* (2000) 424:588–606. doi:10.1002/1096-9861(20000904)424:4<588::AID-CNE3>3.0.CO;2-7
18. Sandu N, Chowdhury T, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). How to apply case reports in clinical practice using surrogate models via example of the trigeminocardiac reflex. *J Med Case Rep* (2016) 10:84. doi:10.1186/s13256-016-0849-z
19. Sandu N, Sadr-Eshkevari P, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). Usefulness of case reports to improve medical knowledge regarding trigemino-cardiac reflex in skull base surgery. *J Med Case Rep* (2011) 5:149. doi:10.1186/1752-1947-5-149

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MINI REVIEW
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Antagonistic and Synergistic Activation of Cardiovascular Vagal and Sympathetic Motor Outflows in Trigeminal Reflexes

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The trigeminal nerve and heart are strongly related through somato-autonomic nervous reflexes that induce rapid changes in cardiovascular function. Several trigeminal reflexes have been described, but the diving and trigeminocardiac reflexes are the most studied. The heart is a target organ dually innervated by the sympathetic and parasympathetic systems. Thus, how cardiac function is regulated during the trigeminal reflexes is the result of the combination of an increased parasympathetic response and increased, decreased, or unaltered sympathetic activity. Various hemodynamic changes occur as a consequence of these alterations in autonomic tone. Often in the oxygen-conserving physiological reflexes such as the diving reflex, sympathetic/parasympathetic co-activation reduces the heart rate and either maintains or increases blood pressure. Conversely, in the trigeminocardiac reflex, bradycardia and hypotension due to parasympathetic activation and sympathetic inactivation tend to be observed. These sudden cardiac innervation disturbances may promote the generation of arrhythmias or myocardial ischemia during surgeries in the trigeminal territory. However, the function and mechanisms involved in the trigeminal reflexes remain to be fully elucidated. The current review provides a brief update and analysis of the features of these reflexes, with special focus on how the autonomic nervous system interacts with cardiovascular function.

Keywords: trigeminocardiac reflex, diving reflex, heart, arrhythmia, myocardial ischemia

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INTRODUCTION

Physiological or pathological stimulation of the trigeminal nerve can trigger sudden cardiovascular disturbances with the characteristic features of a nervous reflex (1). Although these trigeminal reflexes have been thoroughly described in numerous clinical–surgical situations, their physiological and pathophysiological mechanisms, as well as their functional significance, have not been elucidated. In 1908, Aschner (2) and Dagnini (3) described a severe reduction in heart rate as a consequence of eyeball compression (4). In 1975, Kumada et al. described the trigeminal depressor response in an experimental animal model (5). They observed that stimulation of one of the trigeminal branches

or its nuclear sensitive complex triggered a reflex that induced cardiovascular symptoms including a sharp reduction of heart rate, hypotension, apnea, and gastric hypermotility (6, 7). In 1988, Shelly and Church suggested the term "trigeminocardiac reflex" (8), and in 1991, Lang et al. used the term trigeminocardiac reflex to describe intense reflex bradycardia observed in three patients undergoing maxillofacial surgeries (9). In later years, Schaller and colleagues (10, 11) first published the occurrence of a central reflex in humans during cerebellopontine angle and brainstem surgeries and merged these peripheral and central responses into a single autonomic reflex, which is now generally accepted as the trigeminocardiac reflex.

These reflexes represent somato-autonomic responses where the trigeminal nerve is the afferent pathway, the vagus and sympathetic nerves are the efferent pathways, and numerous brainstem nuclei serve as integration centers (12). Although these reflexes share certain anatomical structures, the stimuli by which they are triggered and the responses they elicit are not necessarily equal. The trigeminal reflexes can be triggered by stimuli sensed by thermoreceptors in the facial skin (diving reflex) (13), nasal mucosa (nasopharyngeal reflex) (14), and eyeball (oculocardiac reflex) (4, 15). They can also be activated by direct stimulation of some trigeminal branches and the trigeminal nuclear complex of the brainstem (trigeminocardiac reflex) (16).

TRIGEMINOCARDIAC REFLEX

The trigeminocardiac reflex is a brainstem reflex that has been demonstrated both clinically and experimentally (17). Schaller et al. defined the reflex from a clinical point of view as hypotension with a 20% drop in mean arterial blood pressure and bradycardia lower than 60 beats/min in response to surgical manipulation of the trigeminal nerve trunk or disturbances in the territory of one of its branches. This concept was later redefined by including autonomic symptoms such as a decrease in cardiovascular function less than 20%. This new trigeminocardiac reflex definition is even more inclusive for clinical studies (12). In severe instances, this response can sometimes lead to asystole. They can be classified into two subtypes, depending on which sensory territory is stimulated: the central trigeminocardiac reflex (ganglion to nucleus) and the peripheral trigeminocardiac reflex (peripheral divisions to ganglion). The peripheral trigeminocardiac reflex can be further subdivided into ophthalmocardiac and maxillomandibulocardiac reflexes (16).

In anesthetized rabbits, trigeminal system stimulation reduced heart rate by 13%, mean arterial pressure by 36%, total peripheral vascular resistance by 35%, and cardiac output by a comparatively modest 5%, whereas stroke volume increased by 6% (7). Bilateral vagal section does not reverse hypotension and only partially reverses the decrease in heart rate. This experiment demonstrates that hypotension is independent of heart rate reduction and occurs as a result of vasodilation induced by the sustained decrease in peripheral vascular sympathetic tone. In contrast, heart rate reduction occurs *via* a combination of parasympathetic activation and sympathetic inhibition. Using a different experimental model in rabbits breathing spontaneously, Kumada et al. (6) studied the respiratory effects of electrical stimulation of the spinal trigeminal tract and its nuclei. In this research, a biphasic response could be observed: low frequency and low intensity stimulation produced tachypnea, whereas a slightly more intense stimulation led to expiratory apnea. On the other hand, gastric hypermotility as a consequence of increased vagal tone was also observed, thus constituting itself as an actual trigeminovagal reflex (6) (**Figure 1**). Based on hemodynamic analysis, the trigeminocardiac reflex behaves in a similar manner to the baroreceptor reflexes, in which bradycardia and reduced systemic blood pressure can also be observed as a consequence of vagal activation and sympathetic inhibition (7). As a variant of the trigeminocardiac reflex, the oculocardiac reflex generates the same synergistic sympathetic/parasympathetic output and produces bradycardia and hypotension (**Table 1**).

DIVING REFLEX

Oxygen deprivation, even for brief periods of time, can be highly detrimental. However, many species, such as diving birds, mammals, and even human beings, have adapted to withstand hypoxia or anoxia for longer periods (18). One of the most important physiological adaptations that allow these animals to withstand the lack of oxygen during apnea is the diving reflex (13). Facial submersion in water rapidly triggers a heart rate reduction by vagal activation, an increase in blood pressure by sympathetic hyperactivity, and apnea. In humans, the autonomic response can often be intense: the heart rate can drop to 20–30 beats/min, and the increased peripheral vascular resistance can raise blood pressure to critical levels. This is not observed in other species that are specialized in the art of diving because they are able to maintain blood pressure within physiological ranges despite increased sympathetic tone.

An important modulator of autonomic activity during diving is apnea, which can result by two different mechanisms. First, apnea can occur voluntarily; in this situation, a person consciously inhibits the respiratory centers *via* a centrally induced pathway. An example is simple breath holding. Second, apnea can occur in a reflexive manner following stimulation of cold receptors in the facial skin, eyes, and nasal cavity. At the same time, changes in pulmonary volumes due to apnea can modify the autonomic tone, leading to cardiovascular changes (13). Apnea alone is sufficient to trigger the diving response; however, a greater response is seen when coupled with stimulation of facial cold receptors, as with face immersion. This particularly intense cardiovascular reflex response manifests itself as a consequence of both facial stimulation and apnea. Fagius and Sundlöf studied sympathetic activity in the peroneal nerve and skin of patients after cold water submersion and reported differences in autonomic regulation between muscle and cutaneous blood flow. They observed increased activity of the nerves innervating muscle vessels, accompanied by 30–50% reduction in blood flow as a consequence of higher peripheral vascular resistance (19). However, they also found decreased sympathetic conductivity toward the cutaneous vascular beds, which have a larger role in thermoregulation and sweating. Increased sympathetic tone in

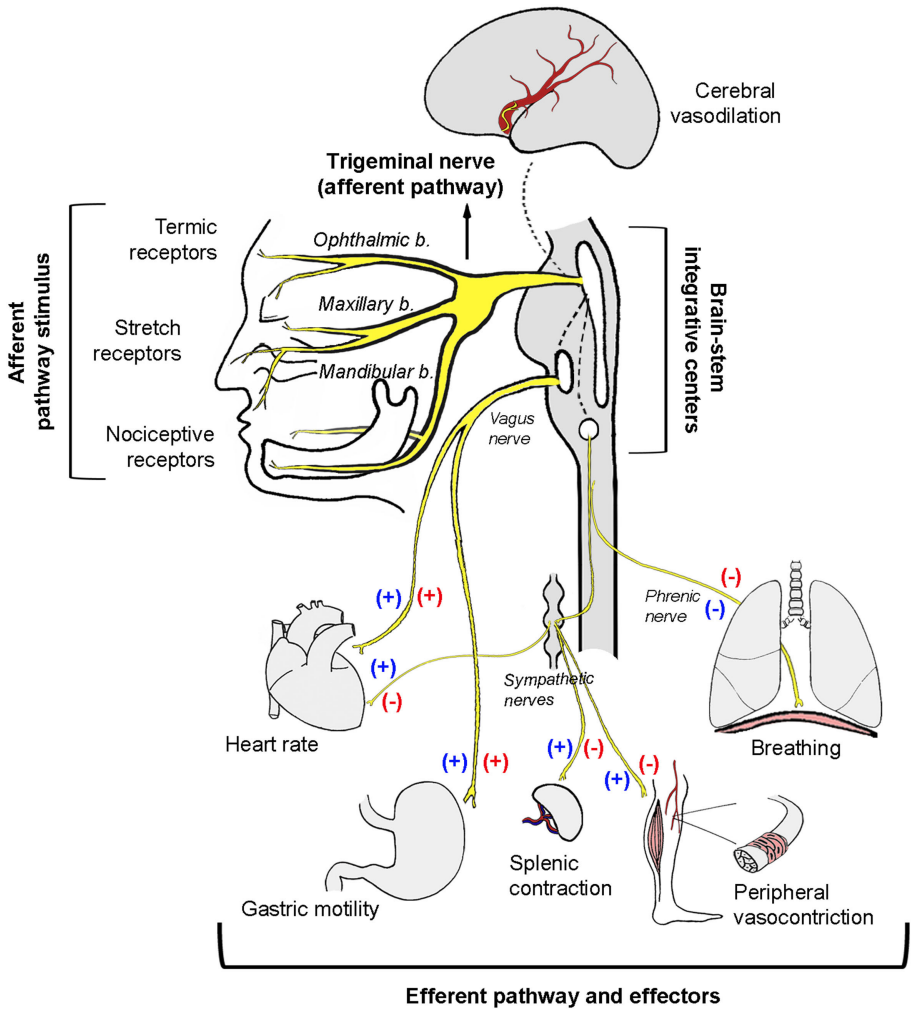

FIGURE 1 | Schematic illustration of the autonomic neural pathways and effectors activated as a consequence of trigeminal nerve stimulation. Protection reflexes like the diving, the nasopharyngeal, or the oculocardiac reflex involve simultaneous co-activation of both autonomic limbs (blue symbols). The trigeminocardiac reflex induces a strong depressor response by a reciprocal activation of the parasympathetic system and an inhibition of the sympathetic system (red symbols).

TABLE 1 | Summary of the principal characteristics of the trigeminal reflex subtypes.

Trigeminal reflex	Triggered by	Efferent pathway	Arterial pressure	Heart rate	Gastric motility	Splenic contraction	Peripheral vascular tone	Breathing
Trigeminocardiac reflex	Direct stimulation of the trigeminal nerve	Parasympathetic ↑ Sympathetic ↓	↓	↓	↑	?	↓	Apnea
Diving reflex	Thermoreceptors in the facial skin	Parasympathetic ↑ Sympathetic ↑	↑	↓	–	↑	↑	Apnea
Nasopharyngeal reflex	Nasal mucosa irritation	Parasympathetic ↑ Sympathetic ↑	=	↓	–	↑	↑	Apnea
Oculocardiac reflex	Physical stimulation of the eye or adnexa	Parasympathetic ↑ Sympathetic ↑	↓	↓	↑	?	↓	Apnea

?, Not known.

the splanchnic vessels and splenic capsule was also observed (18). The contraction of the spleen provides an additional blood volume that aids in stabilizing blood pressure despite the decreased heart rate. Since contraction of the spleen also increases hematocrit and hemoglobin circulating in the blood, it would be expected that oxygen transport would also be enhanced.

The diving reflex in human beings can be modified by many factors, but the most important are water temperature, oxygen

tension in the arterial blood, and emotional factors (20). Previous studies showed a clear inverse relationship between the temperature of the water in which the face is immersed and the magnitude of the diving bradycardia. Interestingly, there may not be a similar close dependence on temperature for the reduction in limb blood flow. With respect to blood oxygen, diving bradycardia is increased if subjects have been breath holding or exercising immediately before performing apnea with face immersion. Such observations suggest the possibility that a reduction in the arterial oxygen tension potentiates the diving reflex. Finally, higher brain functions have profound effects on the development of the diving reflex in humans. When subjects are distracted, diving bradycardia fails to occur despite the face being under water. On the other hand, fear can powerfully accentuate the diving response.

Physiologically, the diving reflex slows down oxygen uptake from the lungs and reduces the rate of arterial blood desaturation, slowing the depletion of both lung and blood oxygen stores. In addition, blood flow is redistributed so that the brain and heart are preferentially perfused. This reduces oxygen delivery to the peripheral capillary beds by stopping blood flow with intense vasoconstriction (18). Therefore, the diving reflex is one of the most powerful somato-autonomic reflexes of the organism, and it is an important life protection mechanism in naturally diving animals. As one might expect, the usual response in the human being, a terrestrial animal, is quantitatively less efficient than that seen in the natural divers.

NASOPHARYNGEAL REFLEX

This is a well-demonstrated variation of the diving reflex, activated by stimulation of the nasal mucosa (14). The nasopharyngeal reflex can be activated by irritating gases, water, or electrical stimulation. The ethmoidal nerve plays an important role in this mechanism by innervating the nasal passages and external nares, and it is fundamental in protecting the upper airway (21, 22). Studies in dogs verified that nasal stimulation increases parasympathetic vagal tone, which reduces heart rate and, consequently, cardiac output. Conversely, the nasopharyngeal reflex increases sympathetic tone, leading to greater peripheral vascular resistance (with the exception of carotid resistance), therefore maintaining stable blood pressure values (23) (**Table 1**). The differential changes in vascular flow at the carotid level suggest blood flow redistribution to the brain. The aforementioned physiological features of the nasopharyngeal reflex demonstrate its role as a powerful oxygen-preserving reflex, similar to the diving reflex.

ANTAGONISM AND SYNERGISM IN SYMPATHETIC/PARASYMPATHETIC INTERACTION

Although the trigeminal reflexes have many aspects in common (e.g., the anatomical substrate), their cardiovascular responses may differ depending on the sympathetic/parasympathetic interaction (24). As already mentioned, the diving reflex elicits strong synergistic co-activation of the sympathetic/parasympathetic systems, allowing for heart rate reduction with concurrent maintenance or increase of peripheral arterial pressure (13, 14). On the other hand, the trigeminocardiac reflex is characterized by parasympathetic activation and sympathetic inhibition, which simultaneously reduce heart rate and blood pressure (6) (**Figure 1**; **Table 1**).

Some studies have clarified the factors that condition trigeminal stimulation responses. First, the type of stimulus triggering the reflex should be taken into consideration. Pressor responses are frequently reported, indicating an increase in the peripheral sympathetic tone in response to physiological stimuli, such as irritation of the nasal mucous membrane (14) or stimulation of the thermal nerve endings of facial skin (25). Conversely, in surgical or experimental stimulations of the trigeminal nerve trunk in anesthetized patients, important reductions can be observed both in sympathetic tone and blood pressure (16). Stimulus intensity, frequency, and duration, as well as the type of afferent nervous fibers involved in the reflexogenic response, should also be taken into account.

The second aspect to consider is the administration of different analgesics and anesthetics that may modulate the trigeminal–vagal reflexes in variable and unpredictable ways (26–29). This is of particular importance for the trigeminocardiac reflex, since numerous studies reported autonomic reaction differences based on the use of these drugs (30). Therefore, anesthesia type and depth are important factors to consider in the clinical management of patients undergoing surgical interventions in the trigeminal territory who are at potential risk of cardiovascular depression (31–33).

The last aspect to consider is species differences. In diving animals such as seals, the diving reflex increases sympathetic tone and allows preservation of blood pressure within physiological ranges. In humans, however, the sympathetic response of the diving reflex is more intense and may increase blood pressure to critical values (30).

HEMODYNAMIC CHANGES DURING TRIGEMINAL REFLEXES

Bradycardia and blood pressure modifications are the most evident hemodynamic changes induced by these reflexes. The sudden changes that occur in these reflexogenic adaptations may impact patients with cardiovascular disease, inducing severe and sometimes lethal complications. Various authors reported complications in patients with coronary disease, and severe arrhythmias such as asystole and ventricular fibrillations as a consequence of the trigeminocardiac reflex during neurosurgeries (34, 35). Although not experimentally demonstrated, coronary spasm might be a key factor in the pathophysiology of these complications. Cholinergic discharge in coronary arteries damaged by atherosclerosis could trigger paradoxical vasoconstriction. Also, the sympathetic co-activations that often occur due to trigeminal reflexes may produce vasospasm and decreased blood flow to the myocardium. This cardiac sympathetic co-activation was studied by Nalivaiko et al. in rabbits *via* electrocardiogram, which confirmed the presence of profound co-activation during the nasopharyngeal reflex (36). Intense

changes in autonomic tone following trigeminal stimulation may engender electrical instabilities, which in turn may predispose patients to arrhythmias and imbalances between myocardial oxygen supply and demand.

We previously demonstrated that short-term vagal electrostimulation in rabbits can generate critical changes in myocardial oxygen consumption in the context of coronary ischemia and reperfusion (37). It is interesting to consider that oxygen consumption may vary intensely, to the point of increasing or reducing infarct size depending on the sympathetic/parasympathetic interaction (38). When vagal activation antagonizes the sympathetic system, both infarct size and oxygen consumption are reduced. However, we observe an opposite situation when the sympathetic system is co-activated during vagus nerve stimulation. This shows how both divisions of the autonomic nervous system interaction is fundamental for correct interpretation of the trigeminal reflexes. Even though by definition a major vagal discharge is present, the sympathetic tone fluctuates between an increase and a decrease. It is therefore a critical variable to consider because it can develop numerous complications that may be catastrophic during medical interventions in the trigeminal nerve territory.

CONCLUSION

Stimulation of the trigeminal nerve or the territories innervated by its branches can trigger deep hemodynamic changes due to neurogenic somato-autonomic responses such as the diving and trigeminocardiac reflexes. Although they can act as extremely efficient oxygen-conserving reflexes, the sudden disturbances of cardiovascular autonomic tone can often generate electrical instabilities, predisposing to cardiac arrhythmias and myocardial ischemia. Differences in hemodynamic responses to trigeminal stimulation depend upon the antagonistic or synergistic interaction of the sympathetic and parasympathetic systems. Future investigations will be needed to understand the molecular mechanisms and functional purposes of the trigeminal reflexes. This knowledge is of paramount importance for appropriate management of patients affected during surgeries in the trigeminal territory.

AUTHOR CONTRIBUTIONS

BB brought the manuscript to fruition through the collection of historical and current trends in trigeminal reflexes and composed early drafts of the manuscript and figure. JK contributed to each section including major revisions, current trends, and research in each aspects of the manuscript. EB and ND contributed to revisions and facilitated with manuscript editing and figure assembly. RG provided critical feedback and manuscript revisions, significant intellectual commentary on the manuscript, and final approval of the version to be published.

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REFERENCES

1. Lemaitre F, Chowdhury T, Schaller B. The trigeminocardiac reflex – a comparison with the diving reflex in humans. *Arch Med Sci* (2015) 11(2):419–26. doi:10.5114/aoms.2015.50974
2. Aschner B. Uber einen bisher noch nicht beschriebenen Reflex vom Auge auf Kreislauf und Atmung Verschwinden des Radialispulses bei Druck auf Auge. *Wien Kiln Wschr* (1908) 21:1529–30.
3. Dagnini G. Intemo ad un riflesso provocato in alcuni emiplegici collo stimolo della come e colla pressione sul bulbo oculare. *Bull Sci Med* (1908) 8:380–1.
4. Blanc VF, Hardy JF, Milot J, Jacob JL. The oculocardiac reflex: a graphic and statistical analysis in infants and children. *Can Anaesth Soc J* (1983) 30:360–9.
5. Kumada M, Dampney RAL, Reis DJ. The trigeminal depressor response: a cardiovascular reflex originating from the trigeminal system. *Brain Res* (1975) 92:485–9. doi:10.1016/0006-8993(75)90335-2
6. Kumada M, Dampney RAL, Reis DJ. The trigeminal depressor response: a novel vasodepressor response originating from the trigeminal system. *Brain Res* (1977) 119:305–26. doi:10.1016/0006-8993(77)90313-4
7. Kumada M, Dampney RAL, Whitnall MH, Reis DJ. Hemodynamic similarities between the trigeminal and aortic vasodepressor responses. *Am J Physiol* (1978) 234:67–73.
8. Shelly MP, Church JJ. Bradycardia and facial surgery (letter). *Anaesthesia* (1988) 43:422. doi:10.1111/j.1365-2044.1988.tb09042.x
9. Lang S, Lanigan DT, van der Wal M. Trigeminocardiac reflexes: maxillary and mandibular variants of the oculocardiac reflex. *Can J Anaesth* (1991) 38(6):757–60. doi:10.1007/BF03008454
10. Schaller B, Probst R, Strebel S, Gratzl O. Trigeminocardiac reflex during surgery in the cerebellopontine angle. *J Neurosurg* (1999) 90:215–20.
11. Schaller B, Cornelius JF, Sandu N, Ottaviani G, Perez-Pinzon MA. Oxygen-conserving reflexes of the brain: the current molecular knowledge. *J Cell Mol Med* (2009) 13(4):644–7. doi:10.1111/j.1582-4934.2009.00659.x
12. Chowdhury T, Mendelowith D, Golanov E, Spiriev T, Arasho B, Sandu N, et al. Trigeminocardiac reflex: the current clinical and physiological knowledge. *J Neurosurg Anesthesiol* (2015) 27(2):136–47. doi:10.1097/ANA.0000000000000065
13. Foster GE, Sheel AW. The human diving response, its function, and its control. *Scand J Med Sci Sports* (2005) 15(1):3–12. doi:10.1111/j.1600-0838.2005.00440.x
14. James JE, De Burgh Daly M. Reflex respiratory and cardiovascular effects of stimulation of receptors in the nose of the dog. *J Physiol* (1972) 220(3):673–96.
15. Allison CE, De Lange JJ, Koole FD, Zuurmond WW, Ros HH, van Schagen NT. A comparison of the incidence of the oculocardiac and oculorespiratory reflexes during sevoflurane or halothane anesthesia for strabismus surgery in children. *Anesth Analg* (2000) 90:306–10.
16. Chowdhury T, Sandu N, Sadr-Eshkevari P, Meuwly C, Schaller B. Trigeminocardiac reflex: current trends. *Expert Rev Cardiovasc Ther* (2014) 12(1):9–11. doi:10.1586/14779072.2014.862498
17. Schaller B, Cornelius JF, Prabhakar H, Koerbel A, Gnanalingham K, Sandu N, et al. The trigemino-cardiac reflex: an update of the current knowledge. *J Neurosurg Anesthesiol* (2009) 21(3):187–95. doi:10.1097/ANA.0b013e3181a2bf22
18. Alboni P, Alboni M, Gianfranchi L. Diving bradycardia: a mechanism of defence against hypoxic damage. *J Cardiovasc Med (Hagerstown)* (2011) 12(6):422–7. doi:10.2459/JCM.0b013e328344bcdc
19. Fagius J, Sundlöf G. The diving response in man: effects on sympathetic activity in muscle and skin nerve fascicles. *J Physiol* (1986) 377:429–43. doi:10.1113/jphysiol.1986.sp016196

20. Gooden BA. Mechanism of the human diving response. *Integr Physiol Behav Sci* (1994) 29(1):6–16.
21. Rybka EJ, McCulloch PF. The anterior ethmoidal nerve is necessary for the initiation of the nasopharyngeal response in the rat. *Brain Res* (2006) 1075(1):122–32. doi:10.1016/j.brainres.2005.12.112
22. Hollandsworth MP, DiNovo KM, McCulloch PF. Unmyelinated fibers of the anterior ethmoidal nerve in the rat co-localize with neurons in the medullary dorsal horn and ventrolateral medulla activated by nasal stimulation. *Brain Res* (2009) 1298:131–44. doi:10.1016/j.brainres.2009.08.077
23. Yu YH, Blessing WW. Cerebral blood flow in rabbits during the nasopharyngeal reflex elicited by inhalation of noxious vapor. *J Auton Nerv Syst* (1997) 66(3):149–53.
24. Gelpi RJ, Buchholz B. The trigeminal nerve and the heart. In: Schaller B, Chowdhury T, editors. *Trigeminocardiac Reflex*. Ámsterdam, Países Bajos: Elsevier (2015). p. 51–64.
25. Khurana RK, Wu R. The cold face test: a non-baroreflex mediated test of cardiac vagal function. *Clin Auton Res* (2006) 16(3):202–7. doi:10.1007/s10286-006-0332-9
26. Hahnenkamp K, Honemann CW, Fischer LG, Durieux ME, Muehlendyck H, Braun U. Effect of different anaesthetic regimes on the oculocardiac reflex during paediatric strabismus surgery. *Paediatr Anaesth* (2000) 10:601–8. doi:10.1111/j.1460-9592.2000.00588.x
27. Oh AY, Yun MJ, Kim HJ, Kim HS. Comparison of desflurane with sevoflurane for the incidence of oculocardiac reflex in children undergoing strabismus surgery. *Br J Anaesth* (2007) 99:262–5. doi:10.1093/bja/aem145
28. Chung CJ, Lee JM, Choi SR, Lee SC, Lee JH. Effect of remifentanil on oculocardiac reflex in paediatric strabismus surgery. *Acta Anaesthesiol Scand* (2008) 52:1273–7. doi:10.1111/j.1399-6576.2008.01745.x
29. Arnold RW, Jensen PA, Kovtoun TA, Maurer SA, Schultz JA. The profound augmentation of the oculocardiac reflex by fast acting opioids. *Binocul Vis Strabismus Q* (2004) 19:215–22.
30. Hanamoto H, Niwa H, Sugimura M, Morimoto Y. Autonomic and cardiovascular effects of pentobarbital anesthesia during trigeminal stimulation in cats. *Int J Oral Sci* (2012) 4(1):24–9. doi:10.1038/ijos.2012.7
31. Choi SH, Lee SJ, Kim SH, Kim JH, Kwon HH, Shin YS, et al. Single bolus of intravenous ketamine for anesthetic induction decreases oculocardiac reflex in children undergoing strabismus surgery. *Acta Anaesthesiol Scand* (2007) 51:759–62. doi:10.1111/j.1399-6576.2007.01329.x
32. Ghai B, Ram J, Makkar JK, Wig J, Kaushik S. Subtenon block compared to intravenous fentanyl for perioperative analgesia in pediatric cataract surgery. *Anesth Analg* (2009) 108:1132–8. doi:10.1213/ane.0b013e318198a3fd
33. Wang X, Gorini C, Sharp D, Bateman R, Mendelowitz D. Anaesthetics differentially modulate the trigeminocardiac reflex excitatory synaptic pathway in the brainstem. *J Physiol* (2011) 589(Pt 22):5431–42. doi:10.1113/jphysiol.2011.215392
34. Swerdlow B, Shuer L, Zelcer J. Coronary vasospasm during percutaneous trigeminal rhizotomy. *Anaesthesia* (1988) 43(10):861–3. doi:10.1111/j.1365-2044.1988.tb05600.x
35. Chowdhury T, Meuwly C, Sandu N, Cappellani RB, Schaller B. Coronary spasm in neurosurgical patients and role of trigeminocardiac reflex. *Neurol Res Int* (2014) 2014:974930. doi:10.1155/2014/974930
36. Nalivaiko E, De Pasquale CG, Blessing WW. Electrocardiographic changes associated with the nasopharyngeal reflex in conscious rabbits: vagosympathetic co-activation. *Auton Neurosci* (2003) 105(2):101–4. doi:10.1016/S1566-0702(03)00048-1
37. Buchholz B, Donato M, Perez V, Deutsch AC, Höcht C, Del Mauro JS, et al. Changes in the loading conditions induced by vagal stimulation modify the myocardial infarct size through sympathetic-parasympathetic interactions. *Pflugers Arch* (2015) 467(7):1509–22. doi:10.1007/s00424-014-1591-2
38. Buchholz B, Donato M, Perez V, Ivalde FC, Höcht C, Buitrago E, et al. Preischemic efferent vagal stimulation increases the size of myocardial infarction in rabbits. Role of the sympathetic nervous system. *Int J Cardiol* (2012) 155(3):490–1. doi:10.1016/j.ijcard.2011.12.082

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Diving Response in Rats: Role of the Subthalamic Vasodilator Area

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Diving response (DR) is a powerful integrative response targeted toward survival of the hypoxic/anoxic conditions. Being present in all animals and humans, it allows to survive adverse conditions like diving. Earlier, we discovered that forehead stimulation affords neuroprotective effect, decreasing infarction volume triggered by permanent occlusion of the middle cerebral artery in rats. We hypothesized that cold stimulation of the forehead induces DR in rats, which, in turn, exerts neuroprotection. We compared autonomic [AP, heart rate (HR), cerebral blood flow (CBF)] and EEG responses to the known DR-triggering stimulus, ammonia stimulation of the nasal mucosa, cold stimulation of the forehead, and cold stimulation of the glabrous skin of the tail base in anesthetized rats. Responses in AP, HR, CBF, and EEG to cold stimulation of the forehead and ammonia vapors instillation into the nasal cavity were comparable and differed significantly from responses to the cold stimulation of the tail base. Excitotoxic lesion of the subthalamic vasodilator area (SVA), which is known to participate in CBF regulation and to afford neuroprotection upon excitation, failed to affect autonomic components of the DR evoked by forehead cold stimulation or nasal mucosa ammonia stimulation. We conclude that cold stimulation of the forehead triggers physiological response comparable to the response evoked by ammonia vapor instillation into nasal cavity, which is considered as stimulus triggering protective DR. These observations may explain the neuroprotective effect of the forehead stimulation. Data demonstrate that SVA does not directly participate in the autonomic adjustments accompanying DR; however, it is involved in diving-evoked modulation of EEG. We suggest that forehead stimulation can be employed as a stimulus capable of triggering oxygen-conserving DR and can be used for neuroprotective therapy.

Keywords: diving response, nasal ammonia stimulation, forehead cold stimulation, autonomic parameters, neuroprotection, subthalamic vasodilator area, electroencephalography

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INTRODUCTION

"Diving response" (DR) is a specialized integrative state of the organism targeted toward survival of potentially hypoxic/anoxic conditions, such as diving (1). Observed in diving animals, archetypal DR consists of the coordinated activation of at least three reflexes: simultaneous activation of parasympathetic and sympathetic systems and respiratory adjustments (2, 3). Activation of these reflexes leads, respectively, to bradycardia (4–10), peripheral vasoconstriction limiting blood supply to muscles and "non-critical" organs (2, 11–15), increase in arterial pressure (2, 16–18), and apnea (12, 18, 19).

Diving response is initiated by the excitation of the ophthalmic division of the trigeminal nerve (2), which innervates nasal mucosa, cornea, forehead, and cerebral dura mater (20, 21). Stimulation of the nasal mucosa by perfusion of water or ammonia vapors through the nasal cavity triggers similar response (6, 22). Direct stimulation of the ethmoidal nerve branching from the ophthalmic division and innervating the nasal mucosa produces DR (23).

Autonomic component of the DR is mediated by the medullary circuitry and preserved in decerebrated animals (12, 24). The afferents of the ethmoidal nerve project to the medullary dorsal horn neurons through the trigeminal ganglion. Medullary dorsal horn neurons issue multiple projections (25). Transsynaptical viral tracing of the ethmoidal nerve projections revealed fibers reaching nucleus tractus solitarii, rostral ventrolateral medulla (RVLM), lateral tegmental field, Kolliker Fuse nucleus, and superior salivatory nucleus (SSN) (1, 26). Sympathetic activation responsible for the pronounced peripheral vasoconstriction seems to be mediated by RVLM (27), which, among others, harbors neurons innervating preganglionic neurons of intermediolateral column of the spinal cord and is critical for the control of sympathetic tone (28). Importantly, stimulation of RVLM produces metabolically independent increase in cerebral blood flow (CBF) (29, 30) and exerts some neuroprotection (Yamamoto and Golanov, unpublished observation). Projections of the medullary dorsal horn neurons receiving ethmoidal nerve afferents are observed in pre-Botzinger and trapezoid nuclei (31), which are known to participate in respiratory regulation (32–34) and may be involved in the apneic component of DR (1). DR-associated bradycardia most probably involves activation of parasympathetic preganglionic neurons of nucleus ambiguus, which receive projections from medullary dorsal horn neurons targeted by ethmoidal afferents (35).

Integral effect of DR is overall decreased oxygen consumption and preservation of vital functioning of heart and brain during apneic period (17, 36–38). DR, an evolutionary ancient mechanism of survival of low-oxygen/anoxic conditions (39–41), presents in all animals (1) and exerts powerful protection against anoxic conditions (42). There are reports of humans who remained submerged under water for prolonged periods of time (over 1 h in some cases) and fully recovered afterward (43–46). Survival after near drowning does not depend on body temperature (45, 47, 48), and the DR is suggested to be an important component of survival (49).

While stimulation of the ethmoidal nerve produces DR (23), its transection does not eliminate DR in rats, suggesting that other branches of the ophthalmic nerve are capable of triggering DR (50). In humans, dipping face into cold water is sufficient to initiate typical DR consisting of hypertension and bradycardia (2, 8, 10, 51, 52). In fact, it was suggested that stimulation of face cold receptors is vital for the "survival" DR response (53). These findings allowed us to hypothesize that forehead stimulation can be neuroprotective. In agreement with this hypothesis, we established that cold or electrical forehead stimulation exerts neuroprotective effects, decreasing the infarction volume induced by permanent middle cerebral artery occlusion in rats (54). We suggested that forehead stimulation is capable to trigger DR and accompanying activation of endogenous neuroprotective system (55). Non-invasive, simply applicable method of activation of the DR opens potential of using its protective properties in clinical settings.

The basic "tri-partite" components of the DR – hypertension, bradycardia, and apnea – seem to be mediated at the medullary level (1, 3, 27). However, this basic circuitry mediating autonomic component of the DR is also under control of suprabulbar structures (56). The suprabulbar components of the DR are not well investigated. Subthalamic vasodilator area (SVA) plays an important role in the hypoxia-induced cerebral vasodilation and affords neuroprotection upon stimulation, as we established earlier (57, 58). We hypothesized that SVA may be involved in suprabulbar regulatory mechanisms of DR. Here, we explored whether cold stimulation of the forehead triggers autonomic responses comparable to those induced by nasal mucosa stimulation with ammonia vapors as a "classic" model of DR and compared the responses to changes evoked by cold stimulation of the glabrous skin of tail base in anesthetized rats, and possible role of SVA in DR mechanisms.

MATERIALS AND METHODS

All experiments were performed in accord with NIH "Guide for the care and use of laboratory animals" and approved by the IACUC of the University of Mississippi Medical Center.

General Procedures

The methods were described in detail in our previous publications (58). In short, experiments were performed in adult male Sprague-Dawley rats (250–300 g), maintained in thermally controlled facilities with 12/12 h light cycle and *ad libitum* access to lab chow and water. Anesthesia was initiated in the induction chamber using 5% isoflurane and maintained during surgery at 2–2.5%. All experiments were conducted under isoflurane level of 1.2–1.5% in mixture of 80% N_2 and 20% O_2. Both femoral arteries were cannulated to monitor arterial pressure and to sample blood for blood gasses. Animals were intubated and ventilated using mechanical ventilator at 50–60 strokes/min. Blood gasses were maintained at normal level (pH 7.46 $\pm$ 0.023; PaO_2: 94.3 $\pm$ 1.1 mmHg; $PaCO_2$: 34.2 $\pm$ 0.8 mmHg) (59). Body temperature was maintained at 37°C using feedback-controlled thermoblanket. Following instrumentation, animals were placed in the stereotaxic frame. The calvarium was exposed through the midline cut and the bone was thinned over the area of 3 mm $\times$ 4 mm over the parietal cortex to place laser Doppler needle probe (Periflux PF3, Perymed). A stainless steel screw was inserted through the bone extradurally 0.5 mm rostral and 1 mm lateral to bregma for EEG recording. Arterial pressure was recorded using strain-gauge pressure transducer. EEG was recorded monopolarly with the reference electrode placed in the muscle caudally to the midline cut. EEG signal was filtered at 0.1–100 Hz. Laser Doppler probe (0.45 mm diameter) was positioned over the thinned bone over the parietal cortex area avoiding visible large vessels, and drop of paraffin oil was placed under the probe to provide optical contact. The probe was left in place till the end of experiment. Regional CBF was recorded

with time constant of 0.2 s and expressed in arbitrary units. After placing the probe, cerebrovascular reactivity was assessed by adding CO_2 to breathing mixture for ~2 min, which increased $PaCO_2$ to ~50–60 mmHg. This maneuver triggered fast elevation of CBF by 60–90%. The test was repeated several times during the experiment. If reactivity was lost, animal was euthanized and excluded from the analysis.

Cold Stimulation

Animal forehead was shaved and small thermocouple was introduced under the skin at the rostral angle of the cut on the top of the head. To induce cold stimulation, 1,1-difluoroethane ("Canned Air") was directly applied to the forehead skin for 5 s. 1,1-difluoroethane is a volatile liquid with a boiling point of −25°C. Upon application, it immediately evaporated and decreased under-skin temperature to a minimum of ~12°C by 15 s after the beginning of application. Temperature gradually returned to the baseline of 35.6°C in ~2 min. Identical stimulation has been applied to the base of the tail. There are no known irritation effects of skin application of the 1,1-difluoroethane besides possible "frostbites," when excessive amount is applied for extended period of time. We did not observe any residual skin effects, such as redness or edema, even after multiple short applications of 1,1-difluoroethane in our experiments.

Ammonium Application

To introduce ammonia vapors into the nasal cavity polyethylene catheter (PE-50) was introduce into the nasal cavity through the nares until it reached nasopharynx. Piece of cotton saturated with 50% solution of ammonia hydroxide was placed near the nostrils, and gentle suction was applied for 5 s to the external end of the nasal catheter to create a slightly negative pressure in the nasopharynx, allowing ammonia vapors to be sucked into the nasal cavity through the nares (3). Cotton ball was removed while suction was continued to evacuate ammonia hydroxide vapors from the nasal cavity. All tests were applied three times in each animal with the 10 min intervals.

Excitotoxic Lesion of Subthalamic Vasodilatory Area

The intrinsic neurons of the SVA were bilaterally destroyed with neurotoxin, ibotenic acid. Rats were anesthetized using face mask and placed in stereotaxic frame. Calvarium was exposed, and, through a burr hole, glass micropipette with the tip diameter of 40–50 μm was inserted at 4.8 mm posterior and 1.5 lateral to bregma to the depth of 7.2 mm. Single injection of 3 nmol of IBO in 20 nl of phosphate buffered saline (PBS) was delivered. After injection pipette was kept in place for additional 5 min to avoid backflow. Symmetrical injection on the other side was performed. After wound closure and recovery from anesthesia, animals were kept in the home cage for 5 days before the experiment. Control animals received injection of PBS. As microinjections of PBS into SVA did not affect baseline or cooling and ammonia response the data obtained in this animals were pooled together with naïve animals.

Histological Procedures

After euthanasia with carbon dioxide, brains were removed and frozen in isopentane and stored at −80°C until analysis. For histological analysis, brains were sectioned at 20 μm thickness at −20°C and stained with thionin. Lesioned sites were identified using anatomical brain atlas (60) (**Figure 6**).

Data Collection and Processing

All data were digitized using ADInstruments digitizer and stored for further analysis. Data processing, including fast Fourier transformation (FFT) of EEG, was performed using LabChart software package. Mean arterial pressure (MAP) was calculated according to the formula: 2/3 diastolic pressure + 1/3 systolic pressure. Cerebrovascular resistance (CVR) was calculated as a ratio between MAP and CBF and expressed as percentage of change relative to the baseline. EEG was normalized as percentage of the total power in 0.1–15 Hz interval. For the study purposes, EEG rhythms were defined as follows: delta rhythm – 0.1–3.0 Hz; theta rhythm – 3.1–7.0 Hz; alpha rhythm 7.1–11.0 Hz; beta rhythm 11.1–15 Hz. Data were expressed as mean ± SEM. For statistical analysis, *t*-test for independent and repeated measures and two-way repeated measures ANOVA with Bonferroni *post hoc* multiple comparisons were used (SPSS). Differences were considered significant at $p < 0.05$.

RESULTS

In 12 animals, response to ammonia vapors passage through the nasal cavity has been analyzed. In response to ammonia vapor passage through the nasal cavity, MAP increased by 17.5 ± 3.3% (from 95.6 to 112.5 mmHg, $p < 0.05$) in 11 ± 1 s and returned to the baseline in 146 s (**Figures 1A** and **4A**). The increase in MAP was accompanied by small and slow increase in heart rate (HR), reaching maximum of 1.7 ± 0.4% (from 359.6 to 365.3 beats/min, $p < 0.05$) in 55 ± 4 s (**Figures 1C** and **4C**). In parallel, CBF demonstrated robust increase by 22.8 ± 3.5% reached in 11 ± 1 s ($p < 0.5$, **Figures 1** and **4B**). Increase in CBF was accompanied by non-significant decrease in CVR by −6.6 ± 3.3% at 34 ± 5 s returning to the baseline in 80 s (**Figures 1D** and **4D**). In response to intranasal ammonia vapor administration, power of EEG delta rhythm significantly decreased by 10.6 ± 5.1% ($p < 0.05$) compared with the background activity. At the same time, theta rhythm power increased by 7.2 ± 3.3% ($p < 0.05$), while alpha and beta rhythm did not change significantly (**Figure 3**).

In the same animals, response to the forehead cooling was tested. Five-second application of cold stimulus to the forehead triggered decrease of the subcutaneous temperature from 35°C to a minimum of 12°C reached in 19 s after the initiation of cooling and returned to the baseline by 157 s. In response to decreased forehead temperature MAP raised by 15.0 ± 2.1% ($p < 0.05$, from 92.8 to 106.7 mmHg) in 7 s when subcutaneous temperature decreased to 16.7°C (**Figures 1A** and **4A**). Increase in MAP was comparable to that observed in response to passage of ammonia ($p > 0.05$). In parallel, HR increased by 2.8 ± 0.5% ($p < 0.05$, from 353.4 to 363.2 beats/min) reaching maximum at 23 s (**Figures 1C** and **4C**). CBF started to increase within 2 s of the beginning of

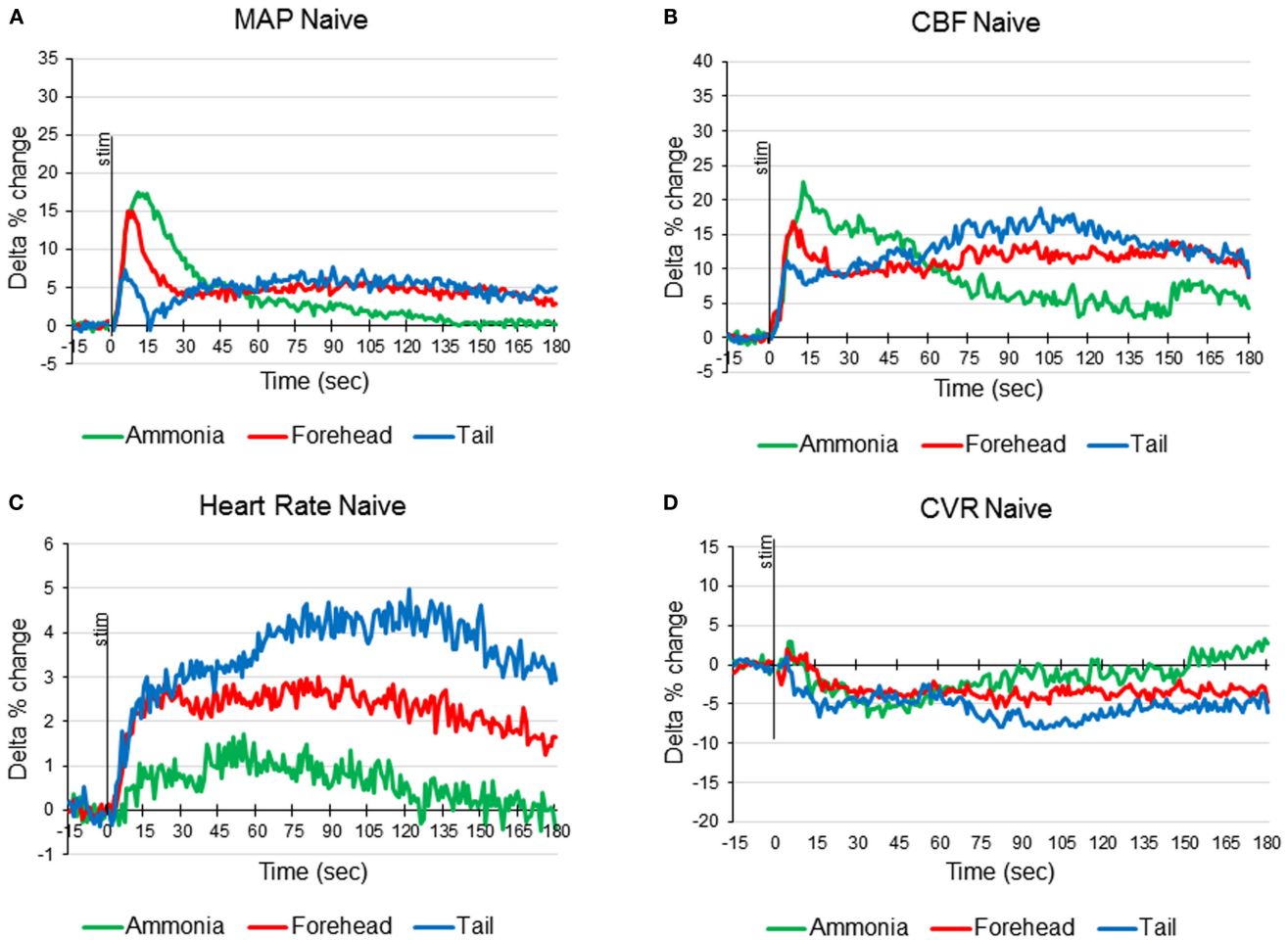

FIGURE 1 | Averaged responses of mean arterial pressure [MAP (A)], cerebral blood flow [CBF (B)], heart rate (C), and cerebrovascular resistance [CVR (D)] to ammonia vapors instillation into the nose (green line), cold stimulation of the forehead (red line), and cold stimulation of the tail base (blue line) in naïve anesthetized artificially ventilated rats expressed as delta percent change compared with baseline (n = 12 animals, 36 tests of each modality).

cooling and reached maximum of 16.8 ± 3.4% ($p < 0.05$) in 9 s. After insignificant increase at 10 s, CVR decreased significantly by 5.5 ± 2.2% ($p < 0.05$) at 81 s (**Figures 1D** and **4D**). All parameters returned to the baseline within 5 min. Forehead cooling did not affect EEG significantly (**Figure 3**).

Comparable 5-s cooling of the tail base triggered biphasic increase in MAP. First, fast increase reached 7.2 ± 2.5% in 6 s (from 92.3 ± 2.4 to 98.9 ± 4.1 mmHg, $p < 0.05$;) followed by the secondary delayed increase by 7.7 ± 2.6% (to 101.7 ± 3.5 mmHg, $p < 0.05$) at 90 s (**Figures 1** and **4A**). MAP returned to the baseline in 5 min. Increases in MAP response to tail base cooling was significantly smaller than responses to ammonia passage or forehead cooling evoked responses. HR in response to tail base cooling was gradual, and, after fast initial increase, it continued to rise reaching maximum of 4.2 ± 1.8% (from 354.4 ± 5.7 to 370.0 ± 9.6 beats/min, $p < 0.05$) by 120 s and returned to the baseline also in 5 min (**Figures 1** and **4C**). CBF increase likewise was biphasic: after peaking in 7 s by 9.8 ± 2.7% ($p < 0.05$), it continued to rise after the short decrease and reached 18.1 ± 3.1% ($p < 0.05$) by 102 s and returned to the baseline in parallel with MAP (**Figures 1** and **4B**). CVR also demonstrate biphasic changes similar to MAP and CBF, the first decrease of −7.0 ± 2.2% (non-significant, n.s.) in 16 s after the stimulus onset was followed by the secondary slightly deeper decrease by −8.1 ± 3.1% ($p < 0.05$) at 111 s. CVR returned to the baseline in parallel with CBF in 5 min (**Figures 1** and **4D**). In response to tail base stimulation, delta rhythm was significantly depressed by 11.1 ± 3.2% ($p < 0.05$) and theta rhythm increased by 9.9 ± 4.4% ($p < 0.05$). Alpha and beta rhythm were not affected significantly (**Figure 3**).

Effects of SVA Lesions

In seven other animals, SVA was lesioned by intraparenchymal injection of ibotenic acid. Histological identification of the localization of lesion of subthalamic vasodilatory area established gliosis in SVA and in the immediate vicinity, including mediate pole of zona incerta, prerubral nucleus, and field of Forel (**Figure 6**). Only animals that demonstrated gliosis in the SVA area were included in the analysis. Baseline absolute values of

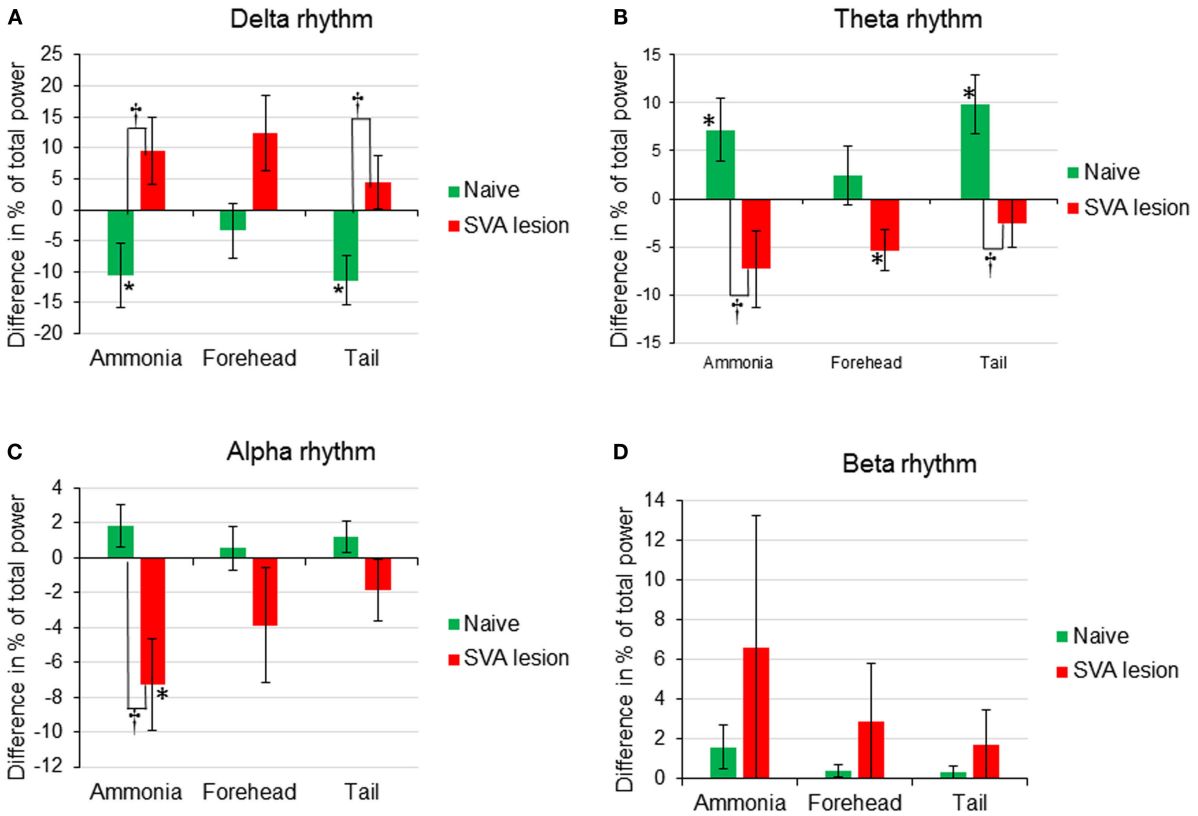

FIGURE 2 | Comparison of changes (difference between percent of total power before and after stimulus) of EEG rhythms [(A) Delta rhythm, (B) Theta rhythm, (C) Alpha rhythm, (D) Beta rhythm] expressed as change in percent of total power in response to nasal ammonia vapor instillation and forehead and tail cold stimulation in naïve (n = 12, green bars) and animals after the lesioning of the subthalamic vasodilator area (n = 7, red bars), *$p < 0.05$ significance of the amplitude of the response compared with the baseline, †$p < 0.05$, significance between response in naive and SVA-lesioned animals, error bars – SEM.

MAP were significantly ($p < 0.05$) higher: 107.3 ± 4.0 mmHg in SVA-lesioned animals compared with 92.7 ± 3.1 mmHg in naïve animals. HR did not differ significantly between naïve and SVA-lesioned animals: 354.5 ± 8.1 beats/min and 360.1 ± 9.1 beats/min, respectively. Baseline EEG was significantly affected by SVA lesion. Background delta rhythm power decreased by 18.2 ± 2.3%, alpha and beta rhythm powers increased by 9.0 ± 2.4% and 6.7 ± 1.9%, respectively ($p < 0.05$), while theta rhythm power did not change significantly (**Figure 5**).

In SVA-lesioned animals, MAP change in response to ammonia passage through the nasal cavities was significantly ($p < 0.05$) facilitated compared with non-lesioned animals and reached 29.3 ± 4.2% (from 106.8 ± 3.9 to 138.5 ± 6.2 mmHg) with that comparable to non-lesioned animals latency of 10 s (**Figures 3A** and **4A**). MAP returned to the baseline within 5 min. HR decreased within 4 s by 1.3 ± 0.6% (from 365.3 to 361.6 beats/min). While the decrease was not significant compared with the baseline it differed significantly when compared with naïve animals, which demonstrated increase in HR (**Figures 3C** and **4C**). CBF response was facilitated reaching 28.6 ± 6.1% ($p < 0.05$), which was not significantly different from the response in naïve animals. However, CBF returned to the baseline significantly faster than in naïve animals within 41 s (**Figures 3B** and **4B**). Following SVA lesion, CVR demonstrated non-significant short increase of 5.3 ± 1.2% in 9 s (**Figures 3D** and **4D**). In response to ammonia passage, only alpha rhythm was significantly suppressed by 7.3 ± 1.2% ($p < 0.05$), while power of other rhythms did not reach level of significance (**Figure 2**).

In response to the forehead cooling in SVA-lesioned animals, MAP increased comparable to the response observed in naïve animals, but, like response to ammonia, was slightly higher and reached 20.2 ± 5.1% ($p < 0.05$) (from 105.7 ± 3.6 to 126.9 ± 4.2 mmHg) of baseline in 6 s and returned to the baseline in 24 s (**Figures 3A** and **4A**). HR in response to the forehead stimulation increased in 6 s by 1.9 ± 0.8% (n.s.) (from 355.61 ± 13.1 to 361.7 ± 10.8 beats/min) followed by secondary increase by 2.5 ± 1.0% (n.s.) (to 363.8 ± 9.5 beats/min) at 40 s which also did not significantly differ from other stimuli and slowly returned to the baseline in 5 min (**Figures 3C** and **4C**). CBF, in response to stimulation, increased in 6 s in parallel to MAP, reaching 19.9 ± 4.5% with secondary increase up to 36.2 ± 6.5% at 136 s and slowly returned to the baseline in 5 min (**Figures 3B** and **4B**). CVR changes in SVA-lesioned animals were amplified compared with naïve animals. CVR in parallel

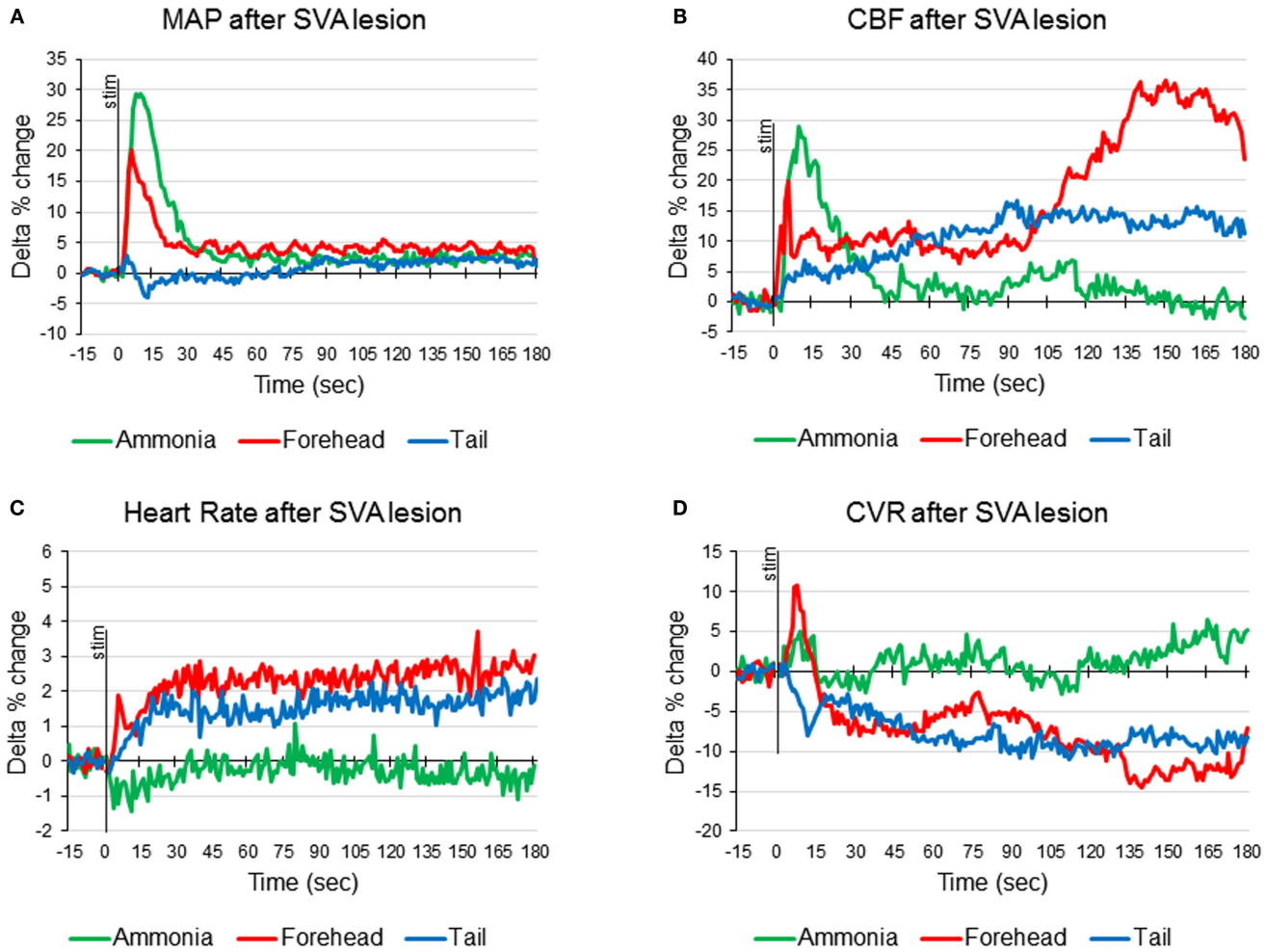

FIGURE 3 | Averaged responses of mean arterial pressure [MAP (A)], cerebral blood flow [CBF (B)], heart rate (C), and cerebrovascular resistance [CVR (D)], to ammonia vapors instillation into the nose (green line), cold stimulation of the forehead (red line), and cold stimulation of the tail base (blue line) in anesthetized artificially ventilated rats after the lesioning of the subthalamic vasodilator area (SVA) (n = 7 animals, 21 tests of each modality).

with CBF increased acutely to 10.8 ± 3.4% ($p < 0.05$) by 8 s and decreased by −7.9 ± 2.6 ($p < 0.05$) at 32 s and further dropped to a minimum of −14.5 ± 4.5% at 140 s, returning to the baseline in 5 min (**Figures 3D** and **4D**). Forehead cooling induced suppression of theta rhythm by 6.4 ± 1.8% ($p < 0.05$), while other rhythms remained unchanged (**Figure 2**).

Response to tail base cold stimulation also was affected in SVA-lesioned animals. Increase in MAP was attenuated and changes were non-significant with the slight increase of 2.3 ± 0.8% (from 107.6 ± 1.2 to 110.1 ± 5.3 mmHg) within 4 s, followed by drop and return to the baseline in 3 min (**Figures 3A** and **4A**). HR increased by 1.9 ± 1.0% at 24 s (from 359.9 ± 9.3 to 365.1 ± 9.6 beats/min), while not reaching significance compared with the background. However, it was significantly ($p < 0.05$) less than in naïve animals (**Figures 3C** and **4C**). CBF response also was attenuated. Initial peak of increase of 6.8 ± 1.4% was reached in 12 s with the secondary increase at 93 s to 16.8 ± % ($p < 0.05$), with gradual return to the baseline in 5 min (**Figures 1**, **2** and **4B**). In parallel, CVR dropped to −8.1 ± % with the further decrease to −14.0 ± 3.5 ($p < 0.05$) in 112 s and returned to the baseline in 5 min (Figure, 1, 2, 4D). Cold stimulation of the tail base failed to significantly modify EEG in SVA-lesioned animals (**Figure 2**).

DISCUSSION

The Model

In our experiments, we explored whether cold stimulation of the forehead is capable to induce DR. We compared autonomic responses triggered by stimulation of the nasal mucosa with ammonia and by cold stimulation of the forehead or the glabrous skin of the tail base. Changes in AP and CBF evoked by ammonia vapors instillation into the nasal cavity or by cold stimulation of the forehead were similar. Both responses, however, differed

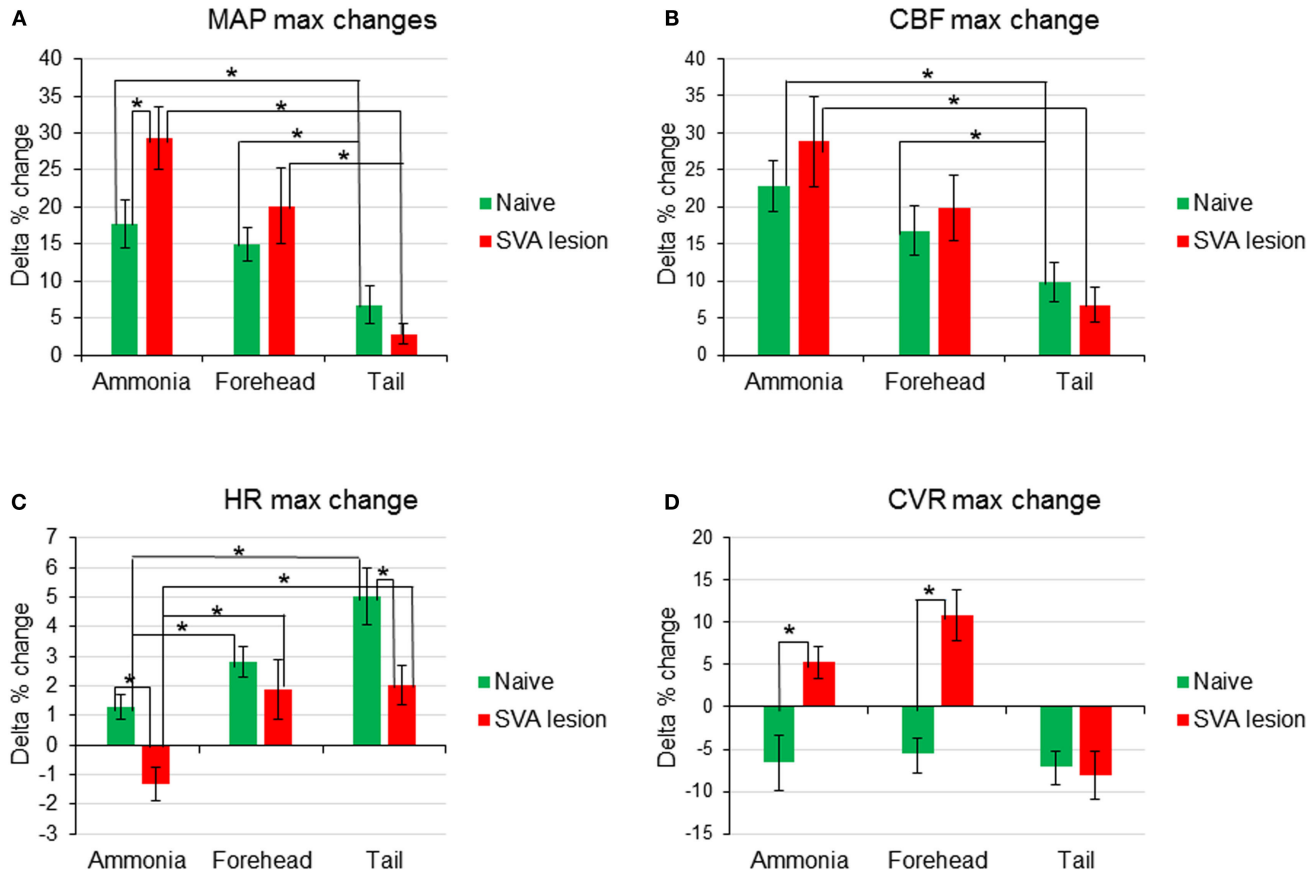

FIGURE 4 | **Comparison of changes of the maximum amplitudes of early responses of mean arterial pressure [MAP (A)], cerebral blood flow [CBF (B)], heart rate [HR (C)], and cerebrovascular resistance [CVR (D)] in response to nasal ammonia vapor instillation and forehead and tail cold stimulation in naïve animals ($n = 12$, green bars) and animals after the lesioning of the subthalamic vasodilator area ($n = 7$, red bars), $^*p < 0.05$, error bars – SEM.**

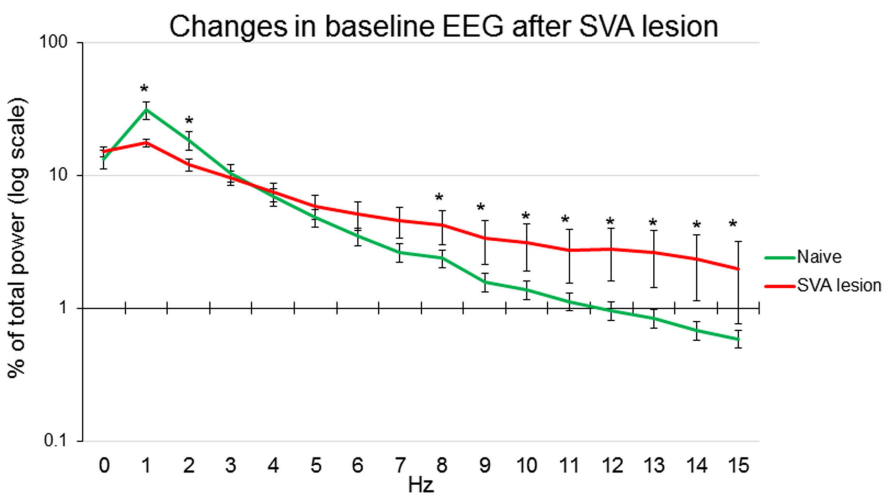

FIGURE 5 | **Power of EEG components expressed as percent of total power in naïve anesthetized artificially ventilated animals ($n = 12$, green line) and in anesthetized artificially ventilated animals after lesion of subthalamic vasodilator area ($n = 7$, red line), $^*p < 0.05$ comparison between naïve and lesioned animals, error bars – SEM.**

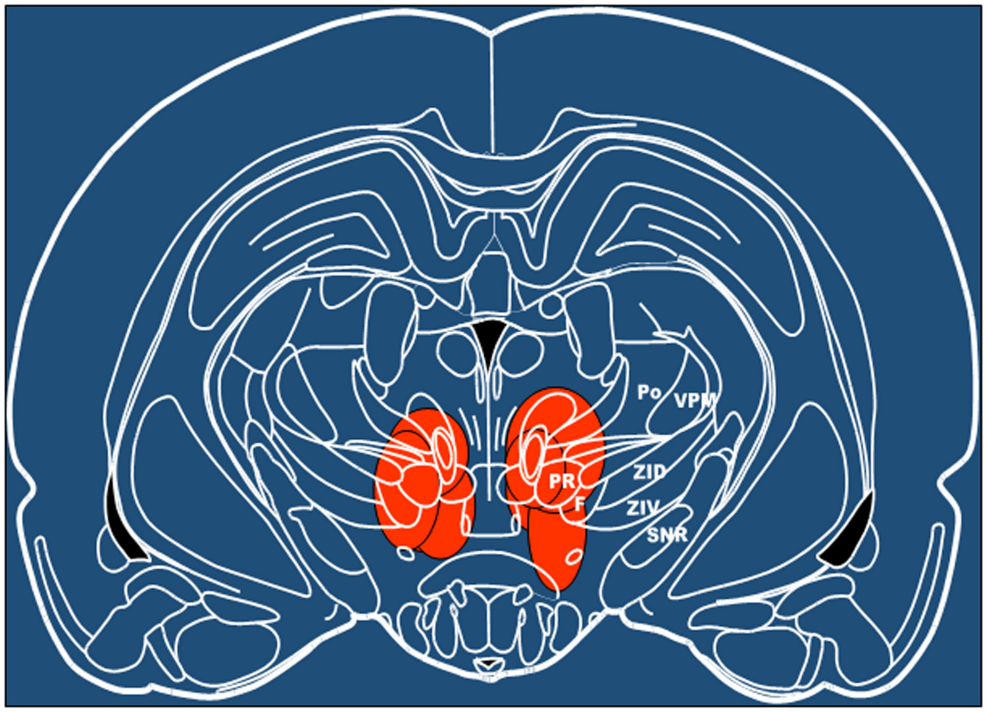

FIGURE 6 | Schematic presentation of areas lesioned by ibotenic acid injection based on the histological analysis. Level −4.8 mm from bregma (60). F, nucleus of the fields of Forel; Po, posterior thalamic nuclear group; PR, prerubral field; SNR, substantia nigra, reticular part; VPM, ventral posteromedial thalamic nucleus; ZID, zona incerta, dorsal part; ZIV, zona incerta, ventral part.

significantly from those induced by cold stimulation of glabrous skin of the tail base.

It is generally accepted that stimulation of the nasal mucosa triggers DR (1, 61–63). The prototypic DR observed in marine animals can be reproduced in other animals, including birds and terrestrial animals. It consists of characteristic and unique triad: hypertension, bradycardia, and apnea, which result from the simultaneous coordinated activation of sympathetic and parasympathetic systems (1, 11, 12). Our experiments demonstrated that MAP, HR, CBF, and CVR responses to the application of the stimuli of different modality, but within the zone innervated by the trigeminal nerve, were comparable. At the same time, the stimuli of the same modality (cold) applied to areas innervated by different nerves, forehead and tale base, produced different responses. These observations suggest that activation of trigeminal system evokes autonomic responses, which differ from responses triggered from other areas. Along with that, some common features between tail and forehead cooling induced responses suggest the existence of shared mechanisms probably related to excitation of somatic cold receptors. Because nasal mucosa stimulation-induced response is considered archetypal DR, we suggest that forehead stimulation also triggers response, which is close if not identical to DR. This conjecture finds support in the observations that, in humans, cold face stimulation triggers autonomic changes, hypertension, and bradycardia, similar to the DR (2, 8, 10, 51, 52).

It is thought that cold stimulation of the ophthalmic branch of trigeminal nerve initiates DR (2). Cold stimulation of the forehead and ammonia nasal mucosal stimulation in our experiments triggered autonomic responses typical for the DR. However, we did not observe bradycardic component of the DR. The weak tachycardic response observed by us probably occurred due to artificial ventilation and isoflurane anesthesia. Lung inflation attenuates bradycardia during DR (64), and isoflurane is capable of decreasing the parasympathetic cardiac drive (65). Simultaneous use of isoflurane in combination with mechanical ventilation in our experiments may negate bradycardic response. This speculation is supported by our observations of pronounced bradycardic responses accompanied by hypertension to electrical stimulation of the forehead in spontaneously respiring rats under isoflurane anesthesia (66, 67). These findings also indicated that apnea plays an important role in the bradycardic component of the DR (68). Overall, it is possible to conclude that forehead cold stimulation triggers autonomic response comparable to DR.

Studies of the mechanisms of the DR are complicated by the various problems related to difficulties of working with diving animals or use of voluntary or forced diving in terrestrial animals (9). Our model allows studying mechanisms of DR in laboratory conditions using various physiological approaches. Use of artificial ventilation provides advantages to explore the mechanism of the DR. First, it obviates heart–lung reflexes (69), which, while a part of the "normal" DR, complicate studies of central

mechanisms responsible for the initiation of the DR. Second, it allows to maintain normal partial pressure of blood gasses and avoids superimposition of chemoreflexes, which also complicate studies of the central mechanism of the DR. Our model of the DR using forehead cold stimulation offers advantages to dissect its central mechanisms.

Changes in Cerebral Blood Flow

It is generally assumed that blood flow to the brain increases during the DR (11, 12). However, limited amount of data are available on the changes of CBF during the DR. Blood flow velocity in the middle cerebral artery in humans increases in response to face cold test (70, 71). Direct stimulation of nasociliary nerve triggers transient increase in CBF (72). Other studies failed to demonstrated changes in CBF related to trigeminal system activation (73, 74). In our model, ammonia nasal stimulation and cold forehead stimulation triggered robust increase in CBF, suggesting that trigeminal stimulation triggers increase in CBF independent of modality. The central mechanisms of the DR include activation of RVLM and nucleus tractus solitarius (NTS) (1). These structures are capable not only to regulate the activity of sympathetic and parasympathetic systems but also induce global neurogenic increase in CBF (75–77). Neurogenic origin of CBF increase is evidenced by the decrease in CVR because mechanisms of autoregulation maintain stable CBF in face of increased MAP by increasing CVR (78). It is conceivable that activation of RVLM also initiates increase in CBF as a part of the DR. However, limited decrease in CVR suggests that, in our model, neurogenic cerebrovasodilation is not the major component of CBF increase and results also from the increase in MAP mediated by excitation of locus coeruleus and Kolliker Fuse nuclei (18). This suggestion is further confirmed by the fact that lesion of SVA mediating RVLM-induced CBF increase (58) failed to do so in our experiments.

Role of Subthalamic Vasodilatory Area

Autonomic components of the DR are mediated by the medullary circuitry (7, 12, 24) as the afferents of the trigeminal ophthalmic branch through the trigeminal ganglion project to NTS, RVLM, lateral tegmental field, Kolliker Fuse nucleus, and SSN (26, 31). Peripheral autonomic reflexes comprising DR (nasotrigeminal reflex) in traditional sense seem to be mediated by the medulla and spinal cord (3). However, this basic circuitry mediating autonomic component of the DR is also under control of suprabulbar structures (56) and regulates brain activity, brain vasculature, and CBF. SVA activation triggers neurogenic metabolically independent increase in CBF evidenced by the decrease in CVR without affecting AP. It also participates in cerebrovasodilation induced by hypoxia (58). Moreover, stimulation of the SVA affords neuroprotection (57). We hypothesized that SVA may participate in the DR mechanisms. However, lesion of SVA did not reverse but augmented increase in MAP and CBF in response to stimulation of nasal mucosa or forehead. HR increase was suppressed (or unchanged in case of the forehead stimulation) and, in response to ammonia application, was even reversed becoming slightly bradycardic. Tail base responses, on the opposite, were suppressed. Interestingly, MAP increase evoked by tail base stimulation was also suppressed. Amplified decrease in delayed, secondary CVR in response to tail stimulation suggests increased neurogenic cerebrovasodilation in response to tail base stimulation following SVA lesion. To summarize, it is possible to suggest that SVA may attenuate sympathetic activation of the heart rate and somatically (tail) induced MAP. At the same time, trigeminally induced changes in AP seem to be potentiated, which explains amplified CBF response. Secondary delayed increase in CBF following forehead cold stimulation and after SVA lesion may relate to release of vasodilatory mediators, such as NO, or prostaglandins and requires further investigation. To conclude, it seems that SVA does not participate directly in trigeminal or somatosensory cerebrovasodilation, but rather modulates these responses. It is conceivable that MAP increase-related increase in CBF is sufficient to provide additional blood supply without neurogenic cerebrovasodilation, which is consistent with the DR-associated "centralization" of circulation. Whether SVA participates in DR-induced neuroprotection (66, 67) remains to be established.

EEG Activity

Limited data are available on the EEG changes accompanying DR. In seals, EEG was changing from alpha low voltage activity to prevalence of high voltage slow waves (79). Apnea alone does not produce significant changes in EEG (80). Trigeminal stimulation has been proposed to suppress seizure-like EEG synchronization (81, 82). In our experiments, ammonia nasal stimulation and tail base stimulation shifted power of EEG frequencies from delta to theta rhythms. Delta rhythm is generally associated with deep non-REM sleep and reflects decreased brain metabolic activity (83). Theta rhythm is observed in various conditions, including general anesthesia, attention, and activity (84). There seems to be two different types of theta rhythm. The first type has higher frequency, can be blocked with atropine, and relates to repeated voluntary behavior. The second type – atropine insensitive – is of lower frequency and relates to general anesthesia or behavioral immobility (85). It was demonstrated that orexin A, synthesized by neurons of lateral hypothalamus promotes wakefulness. Intracerebroventricular administration of orexin A leads to decrease in the power of delta rhythm and simultaneous increase in the power of theta rhythm (86). In our experiments, we observed shift from delta to theta rhythm in response to ammonia nasal stimulation and tail base stimulation. This observation suggests that these stimuli exert short arousal-like effect. Because of anesthesia, full arousal did not occur as evidenced by the lack of alpha desynchronization. Intralaminar and midline thalamic nuclei participate in arousal processes (87). SVA is localized to the posterior midline subthalamic area. Stimulation of this functionally defined area triggers appearance of synchronized EEG activity (58). In our experiments, lesion of SVA significantly suppressed background delta and theta rhythm, while facilitating expression of alpha and beta rhythms. These observations suggest that SVA participates in the maintenance of the specific level of synchronization. At the same time, SVA lesion reversed EEG shift in response to stimuli: power of slow delta rhythm increased while power

of theta rhythm decreased in response to stimuli. These data suggest that SVA participates in the regulation of the synchronization–desynchronization balance. Because lesion of SVA amplified synchronization responses, it seems that SVA is not the leading source of synchronization but rather is a modulator of other structures, which induce cortical synchronization.

CONCLUSION

Our experiments demonstrated similarities between ammonia-induced and forehead cooling-induced response pattern of MAP and CBF. At the same time, these responses differed from somatically (tail base) cold-induced response. These observations suggest that activation of the ophthalmic branch of the trigeminal nerve triggers specific physiological changes compatible with the pattern of "classic" DR observed in animals and humans. Experiments with the lesion of SVA demonstrated that, while SVA does not mediate trigeminal of somatically induced cerebrovasodilation, it modulates these responses and participates in EEG changes accompanying DR. Further investigations of the role of SVA and other elements of endogenous neuroprotective system in DR related neuroprotection are granted.

Diving response directed toward survival of the anoxic periods "is the most powerful and enigmatic reflex" (1). Activation of "oxygen conserving" DR may have beneficial effects in various conditions, such as obstructive sleep apnea, stroke, TBI, and hemorrhagic shock. Our recent experiments indicate that forehead stimulation, indeed, affords neuroprotection following ischemic stroke (54) and traumatic brain injury (66, 67). The present study demonstrates that forehead stimulation triggers response comparable to DR. Further understanding of this complex phenomenon will allow the development of new therapeutic approaches for the various pathologies.

AUTHOR CONTRIBUTIONS

EG designed and performed experiments, analyzed data, and prepared the manuscript. JS performed experiments. GB prepared and edited the manuscript.

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REFERENCES

1. Panneton WM. The mammalian diving response: an enigmatic reflex to preserve life? *Physiology (Bethesda)* (2013) 28:284–97. doi:10.1152/physiol.00020.2013
2. Gooden BA. Mechanism of the human diving response. *Integr Physiol Behav Sci* (1994) 29:6–16. doi:10.1007/BF02691277
3. Panneton WM, Gan Q, Sun DW. Persistence of the nasotrigeminal reflex after pontomedullary transection. *Respir Physiol Neurobiol* (2012) 180:230–6. doi:10.1016/j.resp.2011.11.012
4. Gandevia SC, Mccloskey DI, Potter EK. Reflex bradycardia occurring in response to diving, nasopharyngeal stimulation and ocular pressure, and its modification by respiration and swallowing. *J Physiol* (1978) 276:383–94. doi:10.1113/jphysiol.1978.sp012241
5. Gilbert FF, Gofton N. Heart rate values for beaver, mink and muskrat. *Comp Biochem Physiol A Comp Physiol* (1982) 73:249–51. doi:10.1016/0300-9629(82)90065-2
6. Panneton WM. Trigeminal mediation of the diving response in the muskrat. *Brain Res* (1991) 560:321–5. doi:10.1016/0006-8993(91)91251-U
7. McCulloch PF, Panneton WM. Activation of brainstem catecholaminergic neurons during voluntary diving in rats. *Brain Res* (2003) 984:42–53. doi:10.1016/S0006-8993(03)03051-8
8. Foster GE, Sheel AW. The human diving response, its function, and its control. *Scand J Med Sci Sports* (2005) 15:3–12. doi:10.1111/j.1600-0838.2005.00440.x
9. Panneton WM, Gan Q, Juric R. The rat: a laboratory model for studies of the diving response. *J Appl Physiol* (2010) 108:811–20. doi:10.1152/japplphysiol.00600.2009
10. Alboni P, Alboni M, Gianfranchi L. Diving bradycardia: a mechanism of defence against hypoxic damage. *J Cardiovasc Med* (2011) 12:422–7. doi:10.2459/JCM.0b013e328344bcdc
11. Andersen HT. Physiological adaptations in diving vertebrates. *Physiol Rev* (1966) 46:212–43.
12. Blix AS, Folkow B. Cardiovascular adjustments to diving in mammals and birds. In: Renkin EM, Michel CC, editors. *Sect 2, The Cardiovascular System*. Bethesda: American Physiological Society (1983). p. 917–45.
13. Ferrigno M, Ferretti G, Ellis A, Warkander D, Costa M, Cerretelli P, et al. Cardiovascular changes during deep breath-hold dives in a pressure chamber. *J Appl Physiol* (1997) 83:1282–90.
14. Ollenberger GP, Matte G, Wilkinson AA, West NH. Relative distribution of blood flow in rats during surface and submerged swimming. *Comp Biochem Physiol A Mol Integr Physiol* (1998) 119:271–7. doi:10.1016/S1095-6433(97)00427-3
15. Leuenberger UA, Hardy JC, Herr MD, Gray KS, Sinoway LI. Hypoxia augments apnea-induced peripheral vasoconstriction in humans. *J Appl Physiol* (2001) 90:1516–22.
16. Smith FM, Jones DR. Baroreflex control of arterial blood pressure during involuntary diving in ducks (Anas platyrhynchos var.). *Am J Physiol* (1992) 263:R693–702.
17. de Bruijn R, Richardson M, Schagatay E. Oxygen-conserving effect of the diving response in the immersed human. *Diving Hyperb Med* (2009) 39:193–9.
18. Panneton WM, Gan Q, Le J, Livergood RS, Clerc P, Juric R. Activation of brainstem neurons by underwater diving in the rat. *Front Physiol* (2012) 3:111. doi:10.3389/fphys.2012.00111
19. McCulloch PF. Animal models for investigating the central control of the mammalian diving response. *Front Physiol* (2012) 3:169. doi:10.3389/fphys.2012.00169
20. Waite PME, Tracey DJ. Trigeminal sensory system. Second ed. In: Paxinos G, editor. *The Rat Nervous System*. San Diego, CA: Academic Press (1995). p. 705–24.
21. Waite PME, Ahshwell KWS. Trigeminal sensory sytem. 3rd ed. In: Mai JK, Paxinos G, editors. *The Human Nervous System*. Amsterdam: Elsevier (2012). p. 1110–43.
22. Dormer KJ, Stone HL. Interaction of fastigial pressure response and depressor response to nasal perfusion. *J Auton Nerv Syst* (1980) 2:269–80. doi:10.1016/0165-1838(80)90016-8
23. McCulloch PF, Faber KM, Panneton WM. Electrical stimulation of the anterior ethmoidal nerve produces the diving response. *Brain Res* (1999) 830:24–31. doi:10.1016/S0006-8993(99)01374-8
24. Gabbott GR, Jones DR. The effect of brain transection on the response to forced submergence in ducks. *J Auton Nerv Syst* (1991) 36:65–74. doi:10.1016/0165-1838(91)90131-L
25. Waite PME, Tracey DJ. Trigeminal sensory system. In: Paxinos G, editor. *The Rat Nervous System*. San Diego: Academic Press (2004). p. 815–52.
26. Panneton WM, Mcculloch PF, Sun W. Trigemino-autonomic connections in the muskrat: the neural substrate for the diving response. *Brain Res* (2000) 874:48–65. doi:10.1016/S0006-8993(00)02549-X

27. McCulloch PF, Panneton WM, Guyenet PG. The rostral ventrolateral medulla mediates the sympathoactivation produced by chemical stimulation of the rat nasal mucosa. *J Physiol* (1999) 516(Pt 2):471–84. doi:10.1111/j.1469-7793.1999.0471v.x
28. Guyenet PG, Koshiya N, Huangfu D, Baraban SC, Stornetta RL, Li YW. Role of medulla oblongata in generation of sympathetic and vagal outflows. *Prog Brain Res* (1996) 107:127–44. doi:10.1016/S0079-6123(08)61862-2
29. Underwood MD, Iadecola C, Sved AF, Reis DJ. Stimulation of C1 area neurons globally increases regional cerebral blood flow but not metabolism. *J Cereb Blood Flow Metab* (1992) 12:844–55. doi:10.1038/jcbfm.1992.116
30. Golanov EV, Reis DJ. Nitric oxide and prostanoids participate in cerebral vasodilation elicited by electrical stimulation of the rostral ventrolateral medulla. *J Cereb Blood Flow Metab* (1994) 14:492–502. doi:10.1038/jcbfm.1994.61
31. Panneton WM, Gan Q, Juric R. Brainstem projections from recipient zones of the anterior ethmoidal nerve in the medullary dorsal horn. *Neuroscience* (2006) 141:889–906. doi:10.1016/j.neuroscience.2006.04.055
32. Ezure K, Tanaka I, Saito Y. Activity of brainstem respiratory neurones just before the expiration-inspiration transition in the rat. *J Physiol* (2003) 547:629–40. doi:10.1113/jphysiol.2002.032805
33. Guyenet PG. Regulation of breathing and autonomic outflows by chemoreceptors. *Compr Physiol* (2014) 4:1511–62. doi:10.1002/cphy.c140004
34. Koshiya N, Oku Y, Yokota S, Oyamada Y, Yasui Y, Okada Y. Anatomical and functional pathways of rhythmogenic inspiratory premotor information flow originating in the pre-botzinger complex in the rat medulla. *Neuroscience* (2014) 268:194–211. doi:10.1016/j.neuroscience.2014.03.002
35. Panneton WM, Anch AM, Panneton WM, Gan Q. Parasympathetic preganglionic cardiac motoneurons labeled after voluntary diving. *Front Physiol* (2014) 5:8. doi:10.3389/fphys.2014.00008
36. Wolf S, Groover ME. Neural influences afecting oxygen-conserving (diving) reflex in man. *Fed Proc* (1965) 24:204.
37. Landsberg PG. Bradycardia during human diving. *S Afr Med J* (1975) 49:626–30.
38. Andersson J, Schagatay E. Arterial oxygen desaturation during apnea in humans. *Undersea Hyperb Med* (1998) 25:21–5.
39. Elsner R, Gooden B. Diving and asphyxia. A comparative study of animals and man. *Monogr Physiol Soc* (1983) 40:1–168. doi:10.1017/CBO9780511735714.002
40. Gooden BA. The evolution of asphyxial defense. *Integr Physiol Behav Sci* (1993) 28:317–30. doi:10.1007/BF02690929
41. Hochachka PW. Mechanism and evolution of hypoxia-tolerance in humans. *J Exp Biol* (1998) 201:1243–54.
42. Ramirez JM, Folkow LP, Blix AS. Hypoxia tolerance in mammals and birds: from the wilderness to the clinic. *Annu Rev Physiol* (2007) 69:113–43. doi:10.1146/annurev.physiol.69.031905.163111
43. Schmidt U, Fritz KW, Kasperczyk W, Tscherne H. Successful resuscitation of a child with severe hypothermia after cardiac arrest of 88 minutes. *Prehosp Disaster Med* (1995) 10:60–2. doi:10.1017/S1049023X00041686
44. Huckabee HC, Craig PL, Williams JM. Near drowning in frigid water: a case study of a 31-year-old woman. *J Int Neuropsychol Soc* (1996) 2:256–60. doi:10.1017/S135561770000120X
45. Chochinov AH, Baydock BM, Bristow GK, Giesbrecht GG. Recovery of a 62-year-old man from prolonged cold water submersion. *Ann Emerg Med* (1998) 31:127–31. doi:10.1016/S0196-0644(98)70296-3
46. Perk L, Borger VDB, Berendsen HH, Van't Wout JW. Full recovery after 45 min accidental submersion. *Intensive Care Med* (2002) 28:524. doi:10.1007/s00134-002-1245-2
47. Suominen PK, Korpela RE, Silfvast TG, Olkkola KT. Does water temperature affect outcome of nearly drowned children. *Resuscitation* (1997) 35:111–5. doi:10.1016/S0300-9572(97)00036-1
48. Suominen P, Baillie C, Korpela R, Rautanen S, Ranta S, Olkkola KT. Impact of age, submersion time and water temperature on outcome in near-drowning. *Resuscitation* (2002) 52:247–54. doi:10.1016/S0300-9572(01)00478-6
49. Gooden BA. Why some people do not drown. Hypothermia versus the diving response. *Med J Aust* (1992) 157:629–32.
50. Chotiyanonta JS, Dinovo KM, Mcculloch PF. Bilateral sectioning of the anterior ethmoidal nerves does not eliminate the diving response in voluntarily diving rats. *Physiol Rep* (2013) 1:e00141. doi:10.1002/phy2.141
51. Schuitema K, Holm B. The role of different facial areas in eliciting human diving bradycardia. *Acta Physiol Scand* (1988) 132:119–20. doi:10.1111/j.1748-1716.1988.tb08306.x
52. Brown CM, Sanya EO, Hilz MJ. Effect of cold face stimulation on cerebral blood flow in humans. *Brain Res Bull* (2003) 61:81–6. doi:10.1016/S0361-9230(03)00065-0
53. Paulev PE, Pokorski M, Honda Y, Ahn B, Masuda A, Kobayashi T, et al. Facial cold receptors and the survival reflex "diving bradycardia" in man. *Jpn J Physiol* (1990) 40:701–12. doi:10.2170/jjphysiol.40.701
54. Golanov EV. Forehead stimulation decreases volume of the infarction triggered by permanent occlusion of middle cerebral artery in rats. *J Neurol Stroke* (2015) 2(5):00067. doi:10.15406/jnsk.2015.02.00067
55. Golanov E. The oxygen-conserving potential of the trigeminocardiac reflex. In: Schaller B, Chowdhury T, editors. *Trigeminocardial Reflex*. New York: Elsevier (2015). p. 139–49.
56. Blix AS. Cardiovascular responses to diving. *Acta Physiol Scand Suppl* (1988) 571:61–8.
57. Glickstein SB, Ilch CP, Reis DJ, Golanov EV. Stimulation of the subthalamic vasodilator area and fastigial nucleus independently protects the brain against focal ischemia. *Brain Res* (2001) 912:47–59. doi:10.1016/S0006-8993(01)02602-6
58. Golanov EV, Christensen JRC, Reis DJ. Neurons of a limited subthalamic area mediate elevations in cortical cerebral blood flow evoked by hypoxia and excitation of neurons of the rostral ventrolateral medulla. *J Neurosci* (2001) 21:4032–41.
59. Loeb WF, Quimby FW. *The Clinical Chemistry of Laboratory Animals*. New York: Pergamon Press (1989).
60. Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*. San Diego: Academic Press (1998).
61. Panneton WM. Controlled bradycardia induced by nasal stimulation in the muskrat, Ondatra zibethicus. *J Auton Nerv Syst* (1990) 30:253–63. doi:10.1016/0165-1838(90)90257-J
62. Anton F, Herdegen T, Peppel P, Leah JD. c-FOS-like immunoreactivity in rat brainstem neurons following noxious chemical stimulation of the nasal mucosa. *Neuroscience* (1991) 41:629–41. doi:10.1016/0306-4522(91)90355-R
63. McCulloch PF, West NH. Cardiovascular responses to nasal water flow in rats are unaffected by chemoreceptor drive. *Am J Physiol* (1992) 263:R1049–56.
64. Angell-James JE, Elsner R, De Burgh DM. Lung inflation: effects on heart rate, respiration, and vagal afferent activity in seals. *Am J Physiol* (1981) 240:H190–8.
65. Toader E, Cividjian A, Quintin L. Isoflurane suppresses central cardiac parasympathetic activity in rats: a pilot study. *Minerva Anestesiol* (2011) 77:142–6.
66. Li C, Golanov E, Mehan N, Narayan RK. Trigeminal nerve stimulation as a novel therapy for traumatic brain injury. *Annual Meeting of Congress of Neurological Surgeons*. New Orleans, LA (2015) 742 p.
67. Li C, Golanov E, Mehan N, Narayan RK. Neuroprotective effects of trigeminal nerve stimulation in traumatic brain injury. *2015 Military Health System Research Symposium*. Ft. Lauderdale, FL (2015).
68. Manley L. Apnoeic heart rate responses in humans. A review. *Sports Med* (1990) 9:286–310. doi:10.2165/00007256-199009050-00004
69. De Burgh Daly M. Interactions between respiration and circulation. *Comprehensive Physiology*. Hoboken, NJ: John Wiley & Sons, Inc (2011). p. 529–94.
70. Kjeld T, Pott FC, Secher NH. Facial immersion in cold water enhances cerebral blood velocity during breath-hold exercise in humans. *J Appl Physiol* (2009) 106:1243–8. doi:10.1152/japplphysiol.90370.2008
71. Miyazawa T, Horiuchi M, Ichikawa D, Subudhi AW, Sugawara J, Ogoh S. Face cooling with mist water increases cerebral blood flow during exercise: effect of changes in facial skin blood flow. *Front Physiol* (2012) 3:308. doi:10.3389/fphys.2012.00308
72. Suzuki N, Hardebo JE, Kahrstrom J, Owman C. Effect on cortical blood flow of electrical stimulation of trigeminal cerebrovascular nerve fibres in the rat. *Acta Physiol Scand* (1990) 138:307–16. doi:10.1111/j.1748-1716.1990.tb08851.x
73. Zapol WM, Liggins GC, Schneider RC, Qvist J, Snider MT, Creasy RK, et al. Regional blood flow during simulated diving in the conscious Weddell seal. *J Appl Physiol Respir Environ Exerc Physiol* (1979) 47:968–73.

74. Ollenberger GP, West NH. Contribution of hypercapnia and trigeminal stimulation to cerebrovascular dilation during simulated diving. *Am J Physiol* (1998) 274:R921–30.
75. Golanov EV, Reis DJ. Contribution of oxygen-sensitive neurons of the rostral ventrolateral medulla to hypoxic cerebral vasodilatation in the rat. *J Physiol* (1996) 495:201–16. doi:10.1113/jphysiol.1996.sp021585
76. Golanov EV, Christensen JR, Reis DJ. The medullary cerebrovascular vasodilator area mediates cerebrovascular vasodilation and electroencephalogram synchronization elicited from cerebellar fastigial nucleus in Sprague-Dawley rats. *Neurosci Lett* (2000) 288:183–6. doi:10.1016/S0304-3940(00)01228-3
77. Golanov EV, Reis DJ. Neurons of nucleus of the solitary tract synchronize the EEG and elevate cerebral blood flow via a novel medullary area. *Brain Res* (2001) 892:1–12. doi:10.1016/S0006-8993(00)02949-8
78. Reis DJ, Golanov EV. Autonomic and vasomotor regulation. *Int Rev Neurobiol* (1997) 41:121–49. doi:10.1016/S0074-7742(08)60350-5
79. Elsner R, Shurley JT, Hammond DD, Brooks RE. Cerebral tolerance to hypoxemia in asphyxiated Weddell seals. *Respir Physiol* (1970) 9:287–97. doi:10.1016/0034-5687(70)90077-0
80. Ratmanova P, Semenyuk R, Popov D, Kuznetsov S, Zelenkova I, Napalkov D, et al. Prolonged dry apnoea: effects on brain activity and physiological functions in breath-hold divers and non-divers. *Eur J Appl Physiol* (2016) 116:1367–77. doi:10.1007/s00421-016-3390-2
81. Fanselow EE, Reid AP, Nicolelis MA. Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *J Neurosci* (2000) 20:8160–8.
82. DeGiorgio CM, Fanselow EE, Schrader LM, Cook IA. Trigeminal nerve stimulation: seminal animal and human studies for epilepsy and depression. *Neurosurg Clin N Am* (2011) 22:449–56. doi:10.1016/j.nec.2011.07.001
83. Du F, Zhu XH, Zhang Y, Friedman M, Zhang N, Ugurbil K, et al. Tightly coupled brain activity and cerebral ATP metabolic rate. *Proc Natl Acad Sci U S A* (2008) 105:6409–14. doi:10.1073/pnas.0710766105
84. Pignatelli M, Beyeler A, Leinekugel X. Neural circuits underlying the generation of theta oscillations. *J Physiol Paris* (2012) 106:81–92. doi:10.1016/j.jphysparis.2011.09.007
85. Kramis R, Vanderwolf CH, Bland BH. Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbital. *Exp Neurol* (1975) 49:58–85. doi:10.1016/0014-4886(75)90195-8
86. Toth A, Balatoni B, Hajnik T, Detari L. EEG effect of orexin A in freely moving rats. *Acta Physiol Hung* (2012) 99:332–43. doi:10.1556/APhysiol.99.2012.3.10
87. Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Brain Res Rev* (2002) 39:107–40. doi:10.1016/S0165-0173(02)00181-9

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MINI REVIEW
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Definition and Diagnosis of the Trigeminocardiac Reflex: A Grounded Theory Approach for an Update

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Background: The trigeminocardiac reflex (TCR) is defined as sudden onset of parasympathetic dysrhythmias including hemodynamic irregularities, apnea, and gastric hypermotility during stimulation of sensory branches of the trigeminal nerve. Since the first description of the TCR in 1999, there is an ongoing discussion about a more emergent clinical definition. In this work, the author worked out an approach to such an improved definition.

Methods: In this study, a grounded theory approach was used. Literature about TCR was systematically identified through PubMed (MEDLINE), EMBASE (Ovid SP), and ISI Web of Sciences databases from 1/2005 until 8/2015. TCR was defined as a drop of heart rate (HR) below 60 bpm or 20% to the baseline. A grounded theory approach was used to analyze and interpret the data through a synthesis by the researcher's perspectives, values, and positions.

Results: Out of the included studies, the authors formed available data to an update of the understanding of changes in hemodynamic parameters (HR and blood pressure) in a TCR. According to this update, an HR deceleration should be a constant observation to identify a TCR episode while a drop in blood pressure should probably not being fixed to a certain percentage of decrease.

Conclusion: The here presented working definition improves our understanding of the TCR. It leads the way to a new understanding of the TCR for a proper clinical definition.

Keywords: reflex, trigeminocardiac, trigeminocardiac reflex, reflex, oculocardiac

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INTRODUCTION

The trigeminocardiac reflex (TCR) is a phylogenetic old reflex that manifests as sudden onset of changes in hemodynamic parameters, such as heart rate (HR) and mean arterial blood pressure (MABP), but also apnea and gastric hypermotility during stimulation of any branches of the trigeminal nerve. First observed by Kratschmer in 1870 (1) the *peripheral* variant of the TCR was establishment as Aschner–Dagnini reflex (and later known as oculocardiac reflex) by Aschner and Dagnini in the year 1908 (2). The other pioneers of this field include Kumada and colleagues (described trigeminal-depression response) (3), Shelly and Church (coined the term TCR), both

working on animal models. The senior author first described and established the *central* TCR manifestation in humans during surgery in the cerebellopontine angle in the year 1999 (4). These authors showed a relevant drop of more than 20% in MABP and HR after central stimulation of the trigeminal nerve in 14 out of 125 patients (11%) who underwent tumor surgery in the cerebellopontine angle. In this work, it is given a structured explanation and a relatively simple, but emergent definition of the TCR, therefore, working out—for the first time—the basis to compare further studies (4). Schaller and colleagues also examined the TCR in various clinical variants during the following years (5–23) and developed the nowadays-established classification between the peripheral, central, and ganglion subtype of TCR (24). In this structured classification, the generally best-known oculocardiac reflex is included as a peripheral subtype of the TCR. Since the publication of these first articles in 1999, the better and better-examined phenomenon gained increased interest in neurosurgery and neuroanesthesia, demonstrating in the still gaining number of publications. However, since the first day of research, there does still exist now different new variants of the clinical definition of the TCR as these were all developed on an emergent basis during the last nearly 20 years. Now as more and more papers are describing the various clinical subtypes as well as a underestimated chronic subform of TCR, it is imperative to look for a more detailed definition of TCR again on a more systematic approach and to close this gap in the literature. The aim of this work is to develop, by the help of a grounded theory approach, a working clinical definition that is applicable to all subtypes of TCR.

METHODOLOGY

To gain a better definition of the TCR, a grounded theory approach was used. Wolfswinkel et al. reported about the practical appliance of the grounded theory approach advanced by Strauss and Corbin (25, 26) in the methodical reviewing literature (27) as it is found in the growing number of literature on TCR. They described, "applying grounded theory aims to point to well-rooted and fruitful new links between variables" (p. 2). To gain such more "fruitful new links between variables" we choose the grounded theory literature review method since our objective was to close the gap in the literature and find out a more balanced definition of the TCR that includes all newly found TCR subtypes.

We considered four key issues, namely, sampling, creativity, reflexivity, and precision, as pointed out by Cutcliffe (28) to be fundamental to the use of grounded theory as a research method. However, to create the grounded theory literature review method, the five stage process that Wolfswinkel et al. (27) proposed was adopted: "define," "search," "select" (as all three covered by the literature research) "analyze" and "present" (as both presented in the Section "Result").

Literature Research

The authors conducted a systematic literature research in PubMed (MEDLINE), EMBASE (Ovid SP), and ISI Web of Sciences databases from 1/2005 until 8/2015. Search terms included "Trigeminocardiac reflex," "Trigemino-cardiac reflex," "Trigeminal depressor response," and "Oculocardiac reflex." All publications were included, and reference lists of all included articles were reviewed to identify additional relevant articles.

Definition of the TCR

We defined the occurrence of a TCR episode for the non-restrictive purpose of this study as *bradycardia*; a drop of HR below of 60/min or 20% or more from the baseline and/or asystole. Further, a TCR had to occur in a clinical setting during the surgery and fulfill at least one of the major criteria for a TCR as earlier defined by the authors (plausibility or reversibility) (4, 24). There is a strong need for a detailed description and comprehensible cause–effect relationship (4, 24), for every included case. But for the retrospective design of this study and to consider the different clinical manifestation of the TCR subtypes, hypotension, thus a drop of RR below 90/60 mmHg, 70 mmHg MABP, respectively, was an optional criterion and not required for inclusion.

Additional sample inclusion criteria beyond the time limits and search terms already mentioned included type of article, age, and language: case report or a case series with patients' age from 1 to 99 years old and that are published in English, German, or French. We included all articles that reported a TCR in a clinical setting during surgery as defined earlier. If there was no link to a full-text version available, we tried to contact the author directly; if not successful, we excluded the article. All TCR cases were checked for double publication.

The primary search revealed 486 studies. After having used the inclusion criteria on the primary search result, a total of 45 studies remained to be included in this study.

Grounded Theory

The constructivist grounded theory approach was used (29). Data used through the evaluation process were mainly collected in the literature research. Further opinion leader's ideas and researchers own thinking concepts, developed through working since years in this field, were gathered. Through the whole working process, we noted our ideas, impressions, and concepts in a study diary. The collected data underwent an open, axial, and selective coding process. Out of this process results a model that is developed through a seesaw change between concrete data and a model level, between inductive and deductive thought and between open, axial, and selective codes. Data are therefore co-constructed and colored by the researcher's perspectives, values, and positions. This position takes a middle ground between the realist and postmodernist positions by assuming an "obdurate reality" at the same time as it assumes multiple realities and multiple perspectives on these realities (30).

We have therefore performed the literature review as described earlier. The literature review was completed with summarizing the inadequacies of theoretical frameworks to explain what is going on in the proposed area of study. Then, there was a need of seeking new bodies of literature previously not explored to close the gaps.

Covered Topics

The principal goal of this research was to close the literature gap and to create a working definition that leads to an updated model of TCR definition. It includes all newly described subtypes and new knowledge to the physiological background of this model.

RESULTS

The emerging results based on this grounded theory approach are presented in the following separated by the different topics covered.

The Reflex Arc of the TCR—A Unique Entity

The TCR is triggered by physical and/or chemical stimulation of any of the nerve endings of branches of the fifth cranial nerve. After activation of sensory fibers, the afferent signal is transmitted through the Gasserian ganglion to the sensory nucleus of the trigeminal nerve, located on the floor of the fourth ventricle. The link between the afferent and efferent pathway form small internuncial fibers of the reticular formation; they connect the sensory nucleus of cranial nerve V with the efferent premotor neurons, located primarily in the nucleus ambiguous and the dorsal motor nucleus of vagus nerve (31). Completing this pathway, the activation of cardioinhibitory parasympathetic vagal neurons (5, 32) leads to the clinical manifestation. The connection between afferent and efferent fibers is presumably fully located in the brainstem as experimental studies with decerebrated animals showed a likewise trigeminocardiac potential (5, 33). However, in regard to the afferent pathway, there exist marked differences in subtypes of TCR, which lead to different reflex arcs. The peripherally stimulated TCR is related primarily *via* the spinal nucleus of the trigeminal nerve to the Köliker–Fuse nucleus, whereas the centrally stimulated TCR is conveyed *via* the nucleus of the solitary tract to the lateral parabrachial nucleus (31, 34). Previous studies showed, for the peripheral subtype (see below), a co-activation of the parasympathetic and sympathetic nervous system (35). These findings lead to a model where co-activation results in (sympathetically mediated) normo-/hypertension and (parasympathetically mediated) bradycardia. In this model, in a central subtype is no or at least less strong activation of the sympathetically nerve system (23, 24). This phenomenon explains the classic clinical manifestation, described in 1999 by the senior author (4). It seems that a defect interaction of neurons might play a principal role to be prone to the TCR (36) as it was already suggested in case of the SIDS (37).

Updated Categorization of TCR Leading to a New Working Definition

As an update to the classic categorization that divides the TCR into central, peripheral, and ganglion subtype (24), the updated categories of the TCR are still based on the trigger point's location (23). But a trigger point central to the Gasserian ganglion is now subdivided into a central TCR and a brainstem TCR. De Jong et al. showed in animal studies that injection of noradrenaline bilateral of the brainstem, thus the area of nucleus tractus solitarii, results in a decrease of MABP and HR of anesthetized rats (38). It was also seen that the effect of injected noradrenaline was prevented by a previous injection of the α-adrenergic blocking agent phentolamine, at the same site. The authors, therefore, suggested an inhibitory role of α-adrenoceptors in the nucleus tractus solitarii in the central control of MABP. Further, in clinical settings, there are reports about patients with brainstem trauma suggesting that variances in MABP intervals require an intact brainstem, whereas low frequency ~0.06 ± 0.02 Hz BP rhythms may be preserved by sympathetic spinal circuitry (39–41). This hypothesis remains one of the black spots in TCR research, as, from a clinical point of view, such changes in the brainstem must be present in the TCR case, but it has never been proven.

Likewise, peripheral TCR has also shown a new category, furthermore peripheral, as the classic TCR. The latest research has shown similar reflex arches between TCR and diving reflex (DR) (37). The DR, another phylogenic old brainstem reflex, initiates breath holding, slowing down of HR, decreased cardiac output, peripheral vasoconstriction, and increased MABP (5, 42). Same as the TCR, the DR is often seen in newborns causing a decrease in HR (5–51%) by single facial submersion (43, 44). The DR is triggered by sensory input on the trigeminal nerve and therefore considered as a subgroup of the TCR. In contrast to the TCR, the DR manifests clinically, next to apnea and bradycardia, as hypertension due to a sympathetic vasoconstriction. These findings support the new working definition where a more peripheral trigger point of the trigeminal nerve around its course, results in a stronger activation of the sympathetic nervous system and therefore clinically presents as bradycardia with hypertension (24) or apnea (45).

The Spinal-Cardiac Reflex (SCR)—A New Phenomenon in the TCR Classification Scheme

Chowdhury and Schaller (46) recently described, for the first time, the existence of an SCR during direct or indirect manipulation of the spinal dura during spinal surgery. The mechanical stretch of the spinal dura with its intrinsic and extrinsic innervation was considered the most potent provoking factor in inciting this reflex. As in every reflex, also this SCR has a threshold from which it will be triggered, explaining that not every dural manipulation leads to a reflex response. However, such vasovagal reactions are also a substantial part of the manifestation of either pain/fear/other emotional factors and/or decrease in the venous return due to any reason. The usual manifestation of vasovagal includes bradycardia (parasympathetic activation) and/or hypotension (sympathetic inhibition). In clinical practice, SCR—another potential subgroup of the TCR—caused by acute distension of the dura mater (innervated by V1) other than surgical manipulation, e.g., after aneurysm rupture, can play an important role on the high mortality manifesting early after SAH (42, 47, 48). Based on several observations, it seems that sudden decrease of venous return can activate such pathway (49, 50).

The Definition Criteria for TCR

Trigeminocardiac reflex is commonly defined as a sudden drop in HR and MABP of more than 20% as compared with the baseline values (4). Some articles examined the TCR with less restrictive definitions and asked of an observed reflex accompanied by 10% change in HR and MABP to the baseline (51). As a result of the ongoing discussion about the clinical definition of the TCR, according to a cause–effect relationship, our author group showed in previous research (4, 52) four definition criteria that allow identifying a sudden change in the hemodynamic parameter as TCR (24). We, therefore, defined *two major* (plausibility and reversibility) and *two minor* (repetition and prevention) criteria. An estimated TCR event should fulfill these two principal criteria, but not all the criteria must/can always be required to confirm a TCR. However, the more criteria are present; the more confirmed is a TCR. On the one hand, plausibility requires the event as a direct result of a physical or chemical manipulation (stimulation) of the trigeminal nerve or its peripheral branches. There has to be a direct link in time and action between stimulation and reaction (hemodynamic changes, apnea, and gastric hypermotility). On the other hand, reversibility describes that cease of the inducing stimulus should result in termination of the TCR event. However, in a clinical setting, there are some reports about continuing asystole after ceasing of manipulation that required cardiopulmonary reanimation maybe in a matter of a "point of no return" phenomenon (53). According to the minor criteria, a repetition of the stimulus should provoke the reflex each time, as a matter of ethics, this criterion cannot be evaluated in every TCR case in daily practice but is observed under some circumstances (19, 54). As seen in practice, a lighter and tender manipulation of the fifth cranial nerve can either prevent the occurrence of a TCR or result in less severe symptoms, what is, therefore, the most important preventing procedure. Other, not absolute methods include blocking of the nerve by local anesthetics or prior administration of anticholinergic drugs. It is important to understand that the minor criteria are no absolute criteria because neither repetition nor prevention can be fully guaranteed neither from a clinical nor a pathophysiological point of view.

Clinical Example

The following clinical case is already published (21) but underlines that our new working definition improves the description of the phenomenon TCR.

An otherwise healthy young patient suffered from a trauma on the left eye and developed upper gaze diplopia. A computed tomography scan revealed a fracture of the left-sided orbital floor and minimal soft tissue entrapment. At that time, the patient was managed conservatively. After 1 month, the patient complained of several episodes of dizziness while looking up, palpitations, and having left-sided chest pain. Holter monitoring showed normal sinus rhythm but had multiple premature ventricular complexes. Stress electrocardiography and echocardiography also revealed no abnormality. The patient also started to experience slowing of his pulse rate during sleep and rest. On examination, his resting HR and blood pressure (awake) were 60 bpm and 130/80 mmHg, respectively, and reduced to 50 bpm and 100/60 mmHg, respectively, during sleep. The patient also complained of several episodes of interrupted sleep due to the sudden fluctuation of HR and MABP. These symptoms became progressively worse and after a few months, the patient was operated on for the left-sided fractures of the orbital floor. A couple of days after surgery, the patient's cardiovascular symptoms improved dramatically.

Interpretation

From the clinical course, the here described case of an orbital fracture represents a clear TCR. However, based on the strict definition criteria of 1999 (4) (20% decrease of HR and MABP; cause–effect relationship), a TCR cannot be diagnosed as nocturnal sleep is characterized by a (physiological) prolonged blood pressure decrease. With the more flexible working definition (two major and two minor criteria), a TCR can be diagnosed as three (plausibility, reversibility, and repetition) out of four criteria are fulfilled.

DISCUSSION

The grounded theory approach has led to several important new insights into the definition of the TCR.

A New Working Definition Is Needed

Regarding new findings in categorization and definition criteria, but also with the more and more diverse TCR-related phenomena (46, 55–57), it was evident, that the hitherto established definition of a strict 20% drop in HR and MABP was not suitable for all TCR types anymore. Current research leads to a more flexible working definition that is better adaptable to the now newly existent different TCR subtypes (22, 23, 31, 58, 59) and has helped to close this important gap in the literature.

The Role of HR—Updated

As seen in previous studies, a change in HR at TCR manifestation is described as deceleration in all subgroup of TCR except some reports about a TCR from the Ganglion subtype. No matter in which anatomical location the trigeminal nerve is stimulated, the vagal signal will lead to a slowdown of HR rarely resulting in asystole (22, 60–62). Pathophysiologically, this manifestation is explainable by a strong activation of the parasympathetic nervous system. Cardioinhibitory fibers that form the efferent part of the reflex arc (see above) connect the motor nucleus of the vagus nerve to the myocardium (61). These fibers have their main influence on the atrioventricular nodes and not on the ventricles and therefore a chronotropic effect. An activation of the vagal nerve, the cardioinhibitory fibers respectively, conduct an overbalance of the parasympathetic—over the sympathetic nervous system. As a result, the autonomic nervous system loses its ability to react to changes in MABP in a proper way to ensure the ejection volume for a sufficient distribution of blood. At this point, the TCR can also become symptomatic in conscious patients. These symptoms are mostly seen in the chronic manifestation of the TCR (21, 24, 63). According to the actual doctrine, a change in HR, a deceleration respectively, should be a constant observation to identify a TCR episode.

The Role of MABP—Updated

In an episode of TCR, the MABP is mostly known affected with hypotension. It has been seen that the anatomical location of stimulation around the course of the fifth cranial nerve has major influence if the MABP is increasing or decreasing (24). It seems like the more peripheral a stimulation of the trigeminal nerve, the more increasing and in return, the more central, the more decreasing is the MABP in a TCR episode (24). Highest blood pressures were observed in the DR as a—probably—very peripheral variant of the TCR (23, 37). In the DR, which is triggered by immersion of the head into the cold water, an obligatory increase of MABP (combined with an oxygen economizing bradycardia) is observed. The intensity of hemodynamic changes is proportionally changing with an increase of stimuli (e.g., water temperature) (37). Transforming these observations of MABP to defined criteria, a drop in MABP as criteria for TCR should probably not being fixed to a certain percentage of decrease (on the contrary to the accepted definition criteria of 20% decrease in HR and MABP). Moreover, should the identification of a TCR result out of a flexible surrogate definition model that includes all subtypes of TCR.

With the previous definition, often-reported hypertension in peripheral TRC cases forced those clinical presentations not to be considered as TCR although they fulfilled the major definition criteria (plausibility and reversibility). Further research with an accurate evaluation of changes in parameters during TCR episodes is needed to evaluate the here presented hypotheses that a drop in MABP is only facultative and it is required to develop a new working definition that is applicable in clinical and research setting.

The Limitation of a New Surrogate Model

A model that is based on hemodynamic changes as HR and MABP is limited in the diagnostic reliability. A new, more flexible model includes all TCR episodes that fulfill the conservative inclusion criteria of a 20% drop of HR and MABP. With the adaption to the subtypes with less hypotension (e.g., peripheral and DR), new episodes will and can be identified and declared as TCR. This is, mostly from a clinical point of view, necessary for atypical but not less severe hemodynamic changes. The detection of slight manifestation of TCR, which resembles physiological changes in MABP/HR caused by changes in patients' position, pain reactions, or drugs side-effects, is still a delicate challenge. A model that includes more cases shows automatically more false-positive episodes that are wrongly declared as TCR, while a strict model, on the other hand, risks excluding slight manifestation of TCR and thus underestimate the real number of TCR. A required change of 20% in HR seems from a clinical and research point of view still reasonable. If the here presented hypotheses can be proven in a systematic research, hypotension will further be a criterion to help to identify a potential TCR case but will not be a fundamental phenomenon.

A working definition always covers only a part of the reality, and the here presented attempt is no exception. Shortly, this working definition also needs to be proven in a clinical setting and, if necessary, adjusted to further findings. The main questions that have to be answered, if the here presented working definition is conceptually valid, i.e., do they share the different TCR symptoms as seen in various clinical settings and are they sufficiently reliable to allow consistent translational research. As developed from statistical studies, our model is more useful for a case series as for a single case. A single case is always complicated to put into a working definition; even the current definition does not exclude it.

Practical Application of the Model

In daily practice, a TCR episode can cause severe bradycardia up to asystole and hypotension. Several reports of repetitive TCR in patients lead to the assumption that a more powerful trigger on the trigeminal nerve causes more noticeable hemodynamic changes (37, 54, 64, 65). As an only tender contact with the trigeminal nerve is one of the recommendations to prevent a TCR (31, 52), a diagnostic tool for upcoming, slight TCR episodes is essential. An early detection of TCR cases can help the anesthesiologist to warn the surgeon of probably more severe changes in hemodynamic parameters. The here presented working definition represents the basis of a new thinking model that contributes detecting TCR cases in daily practice. It separates TCR cases from another bradycardic phenomenon with other origins, also needing an entirely different treatment. In such a context, the current model has not only a great importance to refine further clinical studies but also to improve the treatment of our patients directly.

View to the Future

The definition of the TCR is in a continual process. Further research about the hemodynamic changes related to the subtypes is necessary to develop and prove a surrogate definition model for clinical and research setting. As a prominent part of the nowadays knowledge results from analyses of case reports (66), further reports and meta-analyses have major priority to have further insights into the behavior of the TCR. There is a need for continuous flexibility in definition models, in this case, according to the location of the trigger point and the resulting subgroup that helped to explain further details of the TCR.

Conclusion

By a grounded theory approach, the here presented working definition improves our understanding of the TCR; either in research as also in clinics. However, like every assumption, it cannot explain the whole phenomenon. But, the here presented model is a significant step to more detailed and precise understanding of the TCR.

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CM and BS created the conception of the work and performed the data collection and the draft. Together with TC, they analyzed and interpreted the data. All the authors helped with critical revision and final approval.

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REFERENCES

1. Kratschmer F. Über Reflexe von der Nasenschleimhaut auf Atmung und Kreislauf. *Sber Akad Wiss Wien* (1870) 62:147–70.
2. Aschner B. Über einen bisher nicht beschriebenen Reflex vom Auge auf Kreislauf und Atmung: Verschwinden des radialis Pulses bei Druck auf das Auge. *Wien* (1908) 21:1529.
3. Kumada M, Dampney RA, Reis DJ. The trigeminal depressor response: a cardiovascular reflex originating from the trigeminal system. *Brain Res* (1975) 92(3):485–9. doi:10.1016/0006-8993(75)90335-2
4. Schaller B, Probst R, Strebel S, Gratzl O. Trigeminocardiac reflex during surgery in the cerebellopontine angle. *J Neurosurg* (1999) 90(2):215–20. doi:10.3171/jns.1999.90.2.0215
5. Schaller B. Trigeminocardiac reflex. A clinical phenomenon or a new physiological entity? *J Neurol* (2004) 251(6):658–65. doi:10.1007/s00415-004-0458-4
6. Schaller B. Trigemino-cardiac reflex during transsphenoidal surgery for pituitary adenomas. *Clin Neurol Neurosurg* (2005) 107(6):468–74. doi:10.1016/j.clineuro.2004.12.004
7. Schaller B. Trigemino-cardiac reflex during microvascular trigeminal decompression in cases of trigeminal neuralgia. *J Neurosurg Anesthesiol* (2005) 17(1):45–8.
8. Schaller BJ, Buchfelder M. Delayed trigeminocardiac reflex induced by an intraorbital foreign body. *Ophthalmologica* (2006) 220(5):348. doi:10.1159/000094629
9. Schaller B, Buchfelder M. Trigemino-cardiac reflex: a recently discovered "oxygen-conserving" response? The potential therapeutic role of a physiological reflex. *Arch Med Sci* (2006) 2(1):3–5.
10. Schaller BJ. The nasogastric reflex in humans, proposed as a potential cause of upper gastrointestinal symptoms, was previously described as the trigemino-cardiac reflex. *Med Hypotheses* (2007) 69(5):1158. doi:10.1016/j.mehy.2007.05.016
11. Schaller B, Filis A, Buchfelder M. Trigeminocardiac reflex in embolization of intracranial dural arteriovenous fistula. *AJNR Am J Neuroradiol* (2008) 29(7):E55. doi:10.3174/ajnr.A1072
12. Schaller B, Sandu N, Filis A, Buchfelder M. Peribulbar block or topical application of local anaesthesia combined for paediatric strabismus surgery. *Anaesthesia* (2008) 63(10):1142–3; author reply 1143–4. doi:10.1111/j.1365-2044.2008.05693_1.x
13. Schaller BJ, Filis A, Buchfelder M. Trigemino-cardiac reflex in humans initiated by peripheral stimulation during neurosurgical skull-base operations. Its first description. *Acta Neurochir (Wien)* (2008) 150(7):715–7; discussion 717–8. doi:10.1007/s00701-008-1602-1
14. Schaller BJ, Rasper J, Filis A, Buchfelder M. Difference in functional outcome of ipsilateral tinnitus after intraoperative occurrence of the trigemino-cardiac reflex in surgery for vestibular schwannomas. *Acta Neurochir (Wien)* (2008) 150(2):157–60. doi:10.1007/s00701-007-1476-7
15. Schaller B, Sandu N, Filis A, Ottaviani G, Rasper J, Nöethen C, et al. Trigemino-cardiac reflex: the trigeminal depressor responses during skull base surgery. *Clin Neurol Neurosurg* (2009) 111(2):220. doi:10.1016/j.clineuro.2008.09.024
16. Sandu N, Spiriev T, Lemaitre F, Filis A, Schaller B; Trigemino-Cardiac-Reflex-Examination-Group (TCREG). New molecular knowledge towards the trigemino-cardiac reflex as a cerebral oxygen-conserving reflex. *ScientificWorldJournal* (2010) 10:811–7. doi:10.1100/tsw.2010.71
17. Spiriev T, Kondoff S, Schaller B. Trigeminocardiac reflex during temporary clipping in aneurismal surgery: first description. *J Neurosurg Anesthesiol* (2011) 23(3):271–2. doi:10.1097/ANA.0b013e3182204c2c
18. Spiriev T, Kondoff S, Schaller B; Trigemino-Cardiac-Reflex-Examination-Group. Cardiovascular changes after subarachnoid hemorrhage initiated by the trigeminocardiac reflex – first description of a case series. *J Neurosurg Anesthesiol* (2011) 23(4):379–80. doi:10.1097/ANA.0b013e3182312486
19. Spiriev T, Tzekov C, Laleva L, Kostadinova C, Kondoff S, Sandu N, et al. Central trigeminocardiac reflex in pediatric neurosurgery: a case report and review of the literature. *J Med Case Rep* (2012) 6:372. doi:10.1186/1752-1947-6-372
20. Chowdhury T, Cappellani RB, Schaller B; Trigeminocardiac Reflex Examination Group (TCREG). Retrogasserian glycerol rhizolysis: first description of occurrence trigeminocardiac reflex. *J Neurosurg Anesthesiol* (2014) 26(1):86–7. doi:10.1097/ANA.0b013e318297f96a
21. Chowdhury T, Cappellani R, Schaller B. Chronic trigemino-cardiac reflex in patient with orbital floor fracture: role of surgery and first description. *J Neurosurg Anesthesiol* (2014) 26(1):91. doi:10.1097/ANA.0b013e3182a1a691
22. Meuwly C, Chowdhury T, Sandu N, Reck M, Erne P, Schaller B. Anesthetic influence on occurrence and treatment of the trigemino-cardiac reflex: a systematic literature review. *Medicine (Baltimore)* (2015) 94(18):e807. doi:10.1097/MD.0000000000000807
23. Meuwly C, Chowdhury T, Sandu N, Schaller BJ. Meta-areas of the trigeminocardiac reflex within the skull base: a neuroanatomic "thinking" model. *J Neurosurg Anesthesiol* (2016) 28(4):437–8. doi:10.1097/ANA.0000000000000240
24. Meuwly C, Golanov E, Chowdhury T, Erne P, Schaller B. Trigeminal cardiac reflex: new thinking model about the definition based on a literature review. *Medicine (Baltimore)* (2015) 94(5):e484. doi:10.1097/MD.0000000000000484
25. Strauss AL, Corbin JM. *Basics of Qualitative Research Techniques and Procedures for Developing Grounded Theory*. Thousand Oaks: SAGE Publications (1998).
26. Anselm L, Strauss JMC. *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. Thousand Oaks: SAGE Publications (1990).
27. Wolfswinkel J, Furtmueller E, Wilderom C. Using grounded theory as a method for rigorously reviewing literature. *Eur J Inf Syst* (2013) 22(1):45–55. doi:10.1057/ejis.2011.51
28. Cutcliffe JR. Methodological issues in grounded theory. *J Adv Nurs* (2000) 31(6):1476–84. doi:10.1046/j.1365-2648.2000.01430.x
29. Charmaz K. Grounded theory: objectivist and constructivist methods. In: Denzin NK, Lincoln YS, editors. *Handbook of Qualitative Research*. Thousand Oaks, California: Sage Publications, Inc (2000). p. 509–35.
30. Ramalho R, Adams P, Huggard P, Hoare K. Literature review and constructivist grounded theory methodology. *Forum Qual Soc Res* (2015) 16(3):19. doi:10.17169/fqs-16.3.2313
31. Chowdhury T, Mendelowith D, Golanov E, Spiriev T, Arasho B, Sandu N, et al. Trigeminocardiac reflex: the current clinical and physiological knowledge. *J Neurosurg Anesthesiol* (2015) 27(2):136–47. doi:10.1097/ANA.0000000000000065
32. Lang S, Lanigan DT, van der Wal M. Trigeminocardiac reflexes: maxillary and mandibular variants of the oculocardiac reflex. *Can J Anaesth* (1991) 38(6):757–60. doi:10.1007/BF03008454
33. Elsner R, Gooden B. Diving and asphyxia. A comparative study of animals and man. *Monogr Physiol Soc* (1983) 40:1–168. doi:10.1017/CBO9780511735714.002
34. Schaller B, Cornelius JF, Prabhakar H, Koerbel A, Gnanalingham K, Sandu N, et al. The trigemino-cardiac reflex: an update of the current knowledge. *J Neurosurg Anesthesiol* (2009) 21(3):187–95. doi:10.1097/ANA.0b013e3181a2bf22
35. McCulloch PF, Faber KM, Panneton WM. Electrical stimulation of the anterior ethmoidal nerve produces the diving response. *Brain Res* (1999) 830(1):24–31. doi:10.1016/S0006-8993(99)01374-8
36. Dergacheva O, Yamanaka A, Schwartz AR, Polotsky VY, Mendelowitz D. Hypoxia and hypercapnia inhibit hypothalamic orexin neurons in rats. *J Neurophysiol* (2016) 116(5):2250–9. doi:10.1152/jn.00196.2016
37. Lemaitre F, Chowdhury T, Schaller B. The trigeminocardiac reflex – a comparison with the diving reflex in humans. *Arch Med Sci* (2015) 11(2):419–26. doi:10.5114/aoms.2015.50974
38. De Jong W. Noradrenaline: central inhibitory control of blood pressure and heart rate. *Eur J Pharmacol* (1974) 29(1):179–81. doi:10.1016/0014-2999(74)90188-5
39. Novak V, Novak P, deMarchie M, Schondorf R. The effect of severe brainstem injury on heart rate and blood pressure oscillations. *Clin Auton Res* (1995) 5(1):24–30. doi:10.1007/BF01845495
40. Schaller B, Graf R. Hypothermia and stroke: the pathophysiological background. *Pathophysiology* (2003) 10(1):7–35. doi:10.1016/j.pathophys.2003.09.001
41. Schaller B, Graf R. Cerebral ischemia and reperfusion: the pathophysiologic concept as a basis for clinical therapy. *J Cereb Blood Flow Metab* (2004) 24(4):351–71. doi:10.1097/00004647-200404000-00001

42. Golanov EV, Shiflett JM, Britz GW. Diving response in rats: role of the subthalamic vasodilator area. *Front Neurol* (2016) 7:157. doi:10.3389/fneur.2016.00157
43. Pedroso FS, Riesgo RS, Gatiboni T, Rotta NT. The diving reflex in healthy infants in the first year of life. *J Child Neurol* (2012) 27(2):168–71. doi:10.1177/0883073811415269
44. Goksor E, Rosengren L, Wennergren G. Bradycardic response during submersion in infant swimming. *Acta Paediatr* (2002) 91(3):307–12. doi:10.1111/j.1651-2227.2002.tb01720.x
45. Hijdra A, Vermeulen M, van Gijn J, van Crevel H. Rerupture of intracranial aneurysms: a clinicoanatomic study. *J Neurosurg* (1987) 67(1):29–33. doi:10.3171/jns.1987.67.1.0029
46. Chowdhury T, Schaller B. The negative chronotropic effect during lumbar spine surgery: a systemic review and aggregation of an emerging model of spinal cardiac reflex. *Medicine (Baltimore)* (2017) 96(1):e5436. doi:10.1097/MD.0000000000005436
47. Golanov EV, Bovshik EI, Wong KK, Pautler RG, Foster CH, Federley RG, et al. Subarachnoid hemorrhage – induced block of cerebrospinal fluid flow: role of brain coagulation factor III (tissue factor). *J Cereb Blood Flow Metab* (2017). doi:10.1177/0271678X17701157
48. Reis DJ, Golanov EV, Galea E, Feinstein DL. Central neurogenic neuroprotection: central neural systems that protect the brain from hypoxia and ischemia. *Ann N Y Acad Sci* (1997) 835:168–86. doi:10.1111/j.1749-6632.1997.tb48628.x
49. Pollard JB. Cardiac arrest during spinal anesthesia: common mechanisms and strategies for prevention. *Anesth Analg* (2001) 92(1):252–6. doi:10.1097/00000539-200101000-00050
50. Geffin B, Shapiro L. Sinus bradycardia and asystole during spinal and epidural anesthesia: a report of 13 cases. *J Clin Anesth* (1998) 10(4):278–85. doi:10.1016/S0952-8180(98)00028-2
51. Bohluli B, Bayat M, Sarkarat F, Moradi B, Tabrizi MH, Sadr-Eshkevari P. Trigeminocardiac reflex during Le Fort I osteotomy: a case-crossover study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* (2010) 110(2):178–81. doi:10.1016/j.tripleo.2009.12.054
52. Meuwly C, Chowdhury T, Gelpi R, Erne P, Schaller B. The trigeminocardiac reflex: is treatment with atropine still justified? *J Neurosurg Anesthesiol* (2017) 29(3):372–3. doi:10.1097/ANA.0000000000000324
53. Rath GP, Chaturvedi A, Chouhan RS, Prabhakar H. Transient cardiac asystole in transsphenoidal pituitary surgery: a case report. *J Neurosurg Anesthesiol* (2004) 16(4):299–301. doi:10.1097/00008506-200410000-00009
54. Shih YR, Peng SK, Tsai TC, Luk HN, Chiang CE. Repetitive junctional rhythm during forehead-lift surgery – a case report. *Acta Anaesthesiol Taiwan* (2005) 43(2):109–12.
55. Chowdhury T, Schaller B. Chronic trigemino-cardiac reflex: an underestimated truth. *Front Neurol* (2017) 8:22. doi:10.3389/fneur.2017.00022
56. Singh GP, Chowdhury T, Bindu B, Schaller B. Sudden infant death syndrome – role of trigeminocardiac reflex: a review. *Front Neurol* (2016) 7:221. doi:10.3389/fneur.2016.00221
57. Chowdhury T, Schaller B. The role of acute trigemino-cardiac reflex in unusual, non-surgical cases: a review. *Front Neurol* (2016) 7:186. doi:10.3389/fneur.2016.00186
58. Sandu N, Chowdhury T, Sadr-Eshkevari P, Filis A, Arasho B, Spiriev T, et al. Trigeminocardiac reflex during cerebellopontine angle surgery: anatomical location as a new risk factor. *Future Neurol* (2015) 10(1):7–13. doi:10.2217/fnl.14.66
59. Chowdhury T, Schaller B. Key to prevention of bradycardia: be relax postoperatively: a case report. *Medicine (Baltimore)* (2016) 95(22):e3733. doi:10.1097/MD.0000000000003733
60. Shilov V, Astakhov A. Haemodynamic effects of oculocardiac reflex. *Intensive Care Med* (2010) 36:S120. doi:10.1007/s00134-010-1999-x
61. Özçelik D, Toplu G, Türkseven A, Sezen G, Ankarali H. The importance of the trigeminal cardiac reflex in rhinoplasty surgery. *Ann Plast Surg* (2015) 75(2):213–8. doi:10.1097/SAP.0000000000000061
62. Chowdhury T, West M. Intraoperative asystole in a patient undergoing craniotomy under monitored anesthesia care: is it TCR? *J Neurosurg Anesthesiol* (2013) 25(1):92–3. doi:10.1097/ANA.0b013e318277d38a
63. Spiriev T, Tzekov C, Kondoff S, Laleva L, Sandu N, Arasho B, et al. Trigemino-cardiac reflex during chronic subdural haematoma removal: report of chemical initiation of dural sensitization. *JRSM Short Rep* (2011) 2(4):27. doi:10.1258/shorts.2011.010137
64. Chowdhury T, Sandu N, Sadr-Eshkevari P, Meuwly C, Schaller B. Trigeminocardiac reflex: current trends. *Expert Rev Cardiovasc Ther* (2014) 12(1):9–11. doi:10.1586/14779072.2014.862498
65. Chowdhury T, Sandu N, Schaller B, Meuwly C. Peripheral trigeminocardiac reflex. *Am J Otolaryngol* (2013) 34(5):616. doi:10.1016/j.amjoto.2013.05.009
66. Sandu N, Chowdhury T, Schaller BJ; Trigemino-Cardiac Reflex Examination Group (TCREG). How to apply case reports in clinical practice using surrogate models via example of the trigeminocardiac reflex. *J Med Case Rep* (2016) 10(1):84. doi:10.1186/s13256-016-0849-z

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MINI REVIEW
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Trigeminal Cardiac Reflex and Cerebral Blood Flow Regulation

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The stimulation of some facial regions is known to trigger the trigemino-cardiac reflex: the main stimulus is represented by the contact of the face with water. This phenomenon called diving reflex induces a set of reactions in the cardiovascular and respiratory systems occurring in all mammals, especially marine (whales, seals). During the immersion of the face in the water, the main responses are aimed at reducing the oxygen consumption of the organism. Accordingly reduction in heart rate, peripheral vasoconstriction, blood pooling in certain organs, especially the heart, and brain and an increase in blood pressure have been reported. Moreover, the speed and intensity of the reflex is inversely proportional to the temperature of the water: more cold the water, more reactions as described are strong. In the case of deep diving an additional effect, such as blood deviation, has been reported: the blood is sequestered within the lungs, to compensate for the increase in the external pressure, preventing them from collapsing. The trigeminal-cardiac reflex is not just confined to the diving reflex; recently it has been shown that a brief proprioceptive stimulation (10 min) by jaw extension in rats produces interesting effects both at systemic and cerebral levels, reducing the arterial blood pressure, and vasodilating the pial arterioles. The arteriolar dilation is associated with rhythmic diameter changes characterized by an increase in the endothelial activity. Fascinating the stimulation of trigeminal nerve is able to activate the nitric oxide release by vascular endothelial cells. Therefore, the aim of this review was to highlight the effects due to trigeminal cardiac reflex induced by a simple mandibular extension. Opposite effects, such as hypotension, and modulation of cerebral arteriolar tone, were observed, when these responses were compared to those elicited by the diving reflex.

Keywords: trigeminal cardiac reflex, mandibular extension, pial arterioles, vasomotion, brain

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INTRODUCTION

In recent years several clinical studies allowed one to assert that the trigeminal cardiac reflex (TCR) is a clinical phenomenon characterized by hemodynamic perturbations, such as reduction in arterial hypotension, bradycardia, respiratory (apnea), and gastric changes (hypermobility). These effects are triggered by stimulation of any branch of the fifth cranial nerve along its course (Kumada et al., 1975, 1977; Schaller et al., 1999; Schaller, 2004, 2005; Schaller et al., 2009a).

It has been suggested that the TCR is due to sensory nerve endings of the trigeminal nerve. The neuronal signals, originated by these endings, are conducted to the sensory nucleus of the trigeminal nerve, via the Gasserian ganglion, forming the afferent pathway of the reflex arc (White and McRitchie, 1973; Schaller et al., 1999).

This afferent pathway continues along the short internuncial nerve fibers in the reticular formation to connect with the efferent pathway in the motor nucleus of the vagus nerve. Several lines of experimental evidence demonstrate that trigeminally induced cardiovascular reflexes could be mediated initially in the trigeminal nucleus caudalis. Subsequently, the parabrachial nucleus, the rostral ventrolateral medulla oblongata, the dorsal medullary reticular field, and the paratrigeminal nucleus are involved in animal models (White and McRitchie, 1973; Schaller et al., 1999). Because the TCR involves all these structures, it was interesting to evaluate the effects exerted by TCR on the cerebral circulation, because hypotension, and bradycardia could induce cerebral blood flow reduction.

Experimental studies, carried out in rabbits, indicate that TCR represents an expression of a central neurogenic reflex leading to rapid cerebrovascular vasodilation, generated by excitation of oxygen-sensitive neurons in the rostral ventrolateral medulla oblongata (Campbell et al., 1994; Ichinohe et al., 1997; Sires et al., 1998; Schaller, 2004). However, these data have been detected only in the cortex. According to this physiological response, the adjustments of the systemic and cerebral circulations can divert blood to the brain or increase cerebral blood flow.

Several clinical observations indicate that TCR causes changes in cerebral cortex blood flow (White and McRitchie, 1973; Loewinger et al., 1987; Bainton et al., 1990; Kosaka et al., 2000; Burnstine, 2002; Schaller et al., 2007, 2009b). No data, however, have been reported about the influence of TCR on the cerebral blood flow in the short and long term follow up period after the reflex beginning.

TCR EFFECT'S ON CEREBRAL BLOOD FLOW

It is known that TCR occurs during both the peripheral and the central manipulations of the trigeminal nerve (Schaller, 2007). Brunelli et al. showed that a brief proprioceptive stimulation (10 min) by jaw extension causes hypotension and bradycardia in humans (Brunelli et al., 2012).

Successively, Lapi et al. demonstrated that a single mandibular extension (ME), consisting in a submaximal rat mouth opening for 10 min by means of a dilator, is accompanied by an unusually prolonged reduction (about 3 h) of heart rate (HR) and mean arterial blood pressure (MABP) (Lapi et al., 2013, 2014a). This effect was found to be associated with a characteristic and prolonged modulation of cerebral arteriolar tone. At first, vasoconstriction concomitant with the ME stimulus was observed; successively, a prolonged vasodilation occurred, lasting for 3 h, during the entire experimental observation period (Lapi et al., 2013).

Although many aspects related to the underlying mechanisms remain to be explained, some of them are now clear. On one hand, it has been shown that these effects are abolished when the three peripheral trigeminal branches are bilaterally cut, indicating that they may be included among the so-called trigemino-cardiac reflexes (Lapi et al., 2013). These results are in agreement with the studies by Kumada and Schaller who observed that trigeminal nerve stimulations are accompanied by (brief) hypotensive and bradycardic responses in anesthetized rabbits and in humans during neurosurgical intervention, respectively (Kumada et al., 1977; Schaller, 2004; Schaller et al., 2007).

Furthermore, it was observed that these effects depend on the ME stimulation length, i.e., less prolonged and pronounced, when the ME lasted 5 min compared to 10 min stimulation. Finally, it has been shown that the initial brief vasoconstriction response involves an opioid-receptor mediated mechanism, because this response is abolished by the opioid-receptor antagonist naloxone. The subsequent prolonged vasodilation involves a nitric oxide mediated mechanism, because it was blunted by the nitric oxide synthase inhibitor (L-N^G-Nitroarginine methyl ester: L-NAME) (Lapi et al., 2014b). A subsequent *in vitro* study, carried out by Lapi and coworkers, showed an increase in the neuronal nitric oxide synthase (nNOS) expression during and after ME, unable to result in vasodilation during ME. However, an increase in the endothelial nitric oxide synthase (eNOS) expression, 2 h after ME, was demonstrated.

TCR EFFECT'S ON CEREBRAL ARTERIOLAR TONE MODULATION

It is interesting to note that the arterioles display rhythmic variations in diameter, termed vasomotion, triggered by smooth muscle cells; however, the endothelium is able to play a modulatory role on vessel tone (Bertuglia et al., 1999). Analyzing the arteriolar diameter changes on 30 min long-term tracings under baseline conditions and after ME, it was possible to enhance the resolution of the low-frequency components, according to Stefanovska's results in humans (Stefanovska et al., 1999). The frequency components around 1.0, 0.3, 0.1, 0.04 Hz have been related to the heart rate, respiration, intrinsic myogenic activity of vascular smooth muscle cells and neurogenic activity on the vessel wall, respectively. Moreover, the frequency component in the range 0.0095–0.021 Hz appears to be modulated by the vascular endothelium (Kvernmo et al., 1999; D'Addio et al., 2013).

The results by Lapi et al. demonstrate the pial arterioles undergo rhythmic diameter changes in sham-operated rats. In 30 min recordings six frequency components were detected: (1) ULF (endothelial activity NO-independent) 0.005–0.0095 Hz, (2) VLF (endothelial activity NO-dependent): 0.0095–0.021 Hz, (3) ILF (neurogenic activity): 0.021–0.052 Hz, (4) LF (myogenic activity): 0.052–0.145 Hz, (5) HF (respiratory activity): 0.145–2.00 Hz and (6) VHF (heart beat): 2.500–4.000 Hz (Lapi et al., 2014a). This pattern was detected during the whole observation time (over 3 h), while MABP (125 ± 10 mmHg) and HR (330 ± 25 bpm) remained unchanged (**Figure 1A**).

In rats submitted to 10 min ME, under baseline conditions MABP was 130 ± 15 mmHg, HR was 325 ± 30 bpm (p = NS vs. sham operated rats) and rhythmic arteriolar oscillations were not different compared to those observed in sham operated

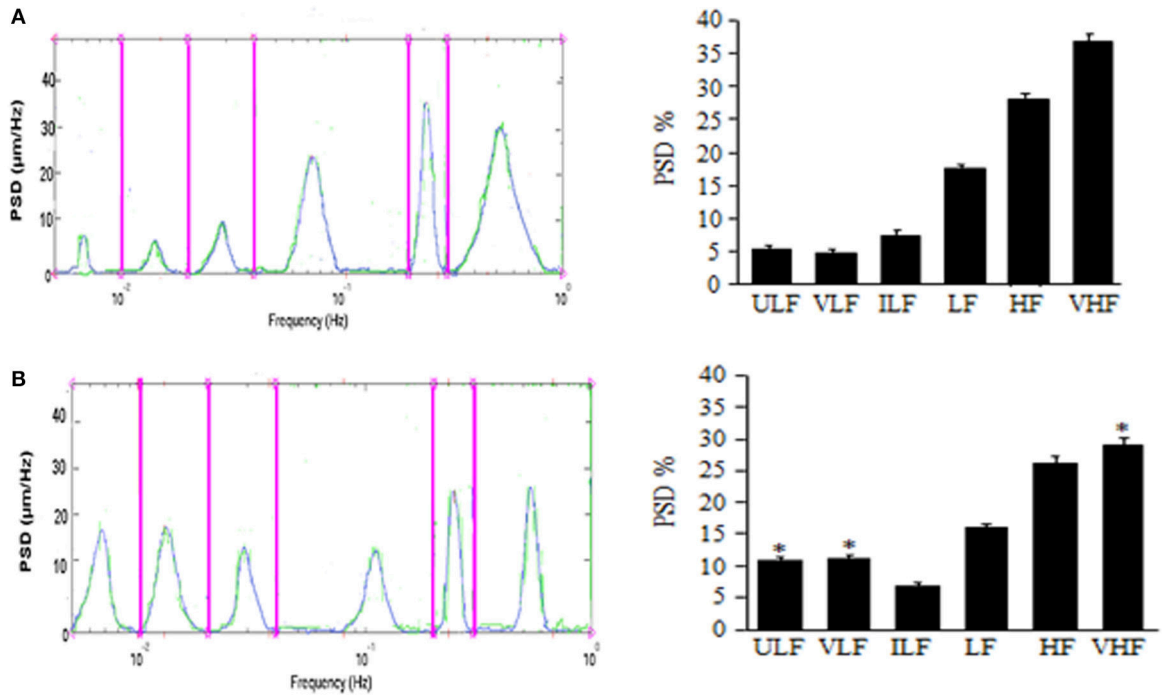

FIGURE 1 | Effects of mandibular extension on rhythmic diameter changes in pial arterioles (mean diameter: 30.0 ± 2.5 μm). Rats subjected to ME, the rhythmic diameter changes (left) and the main corresponding frequency components (right), expressed as percent normalized power spectral density (PSD: μm2/Hz) were measured in baseline conditions **(A)** and during vasodilation **(B)**. ME caused a significant increase of the ULF and VLF frequency components and a decrease of VHF component. ULF, ultra low frequency component; VLF, very low frequency component; ILF, intermediate frequency components; LF, low frequency component; HF, high frequency component ;VHF, very high frequency component. *Significantly different from the baseline value.

rats (Lapi et al., 2014a). After ME, MAP, and HR decreased by 20.5 ± 1.2 and 23.0 ± 0.8% of baseline, respectively; conversely, the amplitude of the first and second frequency components increased: ULF by 7.0 ± 1.5% and VHF by 8.0 ± 2.0% of baseline (**Figure 1B**). Concomitantly, the other frequency components decreased compared with those detected under baseline conditions. These effects lasted up to 3 h after ME (Lapi et al., 2013).

Therefore, a brief (10 min) and passive ME causes a significant and prolonged decrease in MABP and HR, accompanied by an increase in pial arteriolar diameter according to previously reported data (Lapi et al., 2013). Vasodilation is characterized by an increase in the spectral density of the lowest frequencies related to endothelial activity, ULF and VLF (ranges: 0.005–0.0095 Hz and 0.0095–0.021 Hz, respectively).

ME appears to affect the mechanisms involved in the regulation of pial arteriolar tone for long time, likely facilitating the perfusion of cerebral tissue through a modulation of the rhythmic arteriolar diameter changes.

Up to day, the mechanisms whereby ME is accompanied by a prolonged reduction in blood pressure and heart rate remain uncertain. However, ME-induced hypotension may fall into the category of the so-called trigemino-cardiac reflexes extensively reviewed by Schaller (Schaller, 2007). TCR has been proposed to represent the expression of a neuroprotective central neurogenic reflex leading to rapid cerebrovascular vasodilatation in response to facial and nasal mucosal stimulation, such as during diving. Moreover, the reflex may be of potential relevance in brain injury states (Schaller, 2004). Finally, TCR induced by ME as well as the systemic responses, related to activation of vagal efferent discharge, affect the mechanisms involved in the regulation of pial arteriolar tone, increasing the endothelial activity, and facilitating the redistribution of cerebral blood flow supply.

In conclusion, these deep insights into cerebral hemodynamics changes during TCR could stimulate clinical trials and could suggest the development of suitable non-invasive devices, useful in the treatment of disease with impaired cerebral arteriolar tone.

AUTHOR CONTRIBUTIONS

DL: substantial contributions to the conception, analysis and interpretation of data for the work. DL, RS, AC: revising it critically for important intellectual content. AC: Final approval of the version to be published.

REFERENCES

Bainton, R., Barnard, N., Wiles, J. R., and Brice, J. (1990). Sinus arrest complicating a bitemporal approach to the treatment of pan-facial fractures. *Br. J. Oral Maxillofac. Surg.* 28, 109–110. doi: 10.1016/0266-4356(90)90134-7

Bertuglia, S., Colantuoni, A., and Intaglietta, M. (1999). "Regulation of vascular tone and capillary perfusion," in *Texbook of Angiology,* ed J. B. Chan (New York, NY: Springer-Verlag), 439–454.

Brunelli, M., Coppi, E., Tonlorenzi, D., Del Seppia, C., Lapi, D., Colantuoni, A., et al. (2012). Prolonged hypotensive and bradycardic effects of passive mandibular extension: evidence in normal volunteers. *Arch. Ital. Biol.* 150, 231–237. doi: 10.4449/aib.v150i4.1420

Burnstine, M. A. (2002). Clinical recommendations for repair of isolated orbital floor fractures: an evidence-based analysis. *Ophthalmology* 109, 1207–1210. doi: 10.1016/S0161-6420(02)01057-6

Campbell, R., Rodrigo, D., and Cheung, L. (1994). Asystole and bradycardia during maxillofacial surgery. *Anesth. Prog.* 41, 13–16.

D'Addio, G., Cesarelli, M., Iuppariello, L., Lapi, D., and Colantuoni, A. (2013). "Effects of wavelets analysis on power spectral distributions," in *Laser Doppler Flowmetry Time Series IFMBE Proceedings* (Naples), 647–650.

Ichinohe, T., Agata, H., Aida, H., and Kaneko, Y. (1997). Cerebral cortex regional blood flow and tissue oxygen tension during the trigeminal depressor response in rabbits. *J. Auton. Nerv. Syst.* 66, 111–118. doi: 10.1016/S0165-1838(97)00076-3

Kosaka, M., Asamura, S., and Kamiishi, H. (2000). Oculocardiac reflex induced by zygomatic fracture; a case report. *J. Craniomaxillofac. Surg.* 28, 106–109. doi: 10.1054/jcms.2000.0107

Kumada, M., Dampney, R. A., and Reis, D. J. (1975). The trigeminal depressor response: a cardiovascular reflex originating from the trigeminal system. *Brain Res.* 92, 485–489. doi: 10.1016/0006-8993(75)90335-2

Kumada, M., Dampney, R. A., and Reis, D. J. (1977). The trigeminal depressor response: a novel vasodepressor response originating from the trigeminal system. *Brain Res.* 119, 305–326. doi: 10.1016/0006-8993(77)90313-4

Kvernmo, H. D., Stefanovska, A., Kirkeboen, K. A., and Kvernebo, K. (1999). Oscillations in the human cutaneous blood perfusion signal modified by endothelium-dependent and endothelium-independent vasodilators. *Microvasc. Res.* 57, 298–309. doi: 10.1006/mvre.1998.2139

Lapi, D., Colantuoni, A., Del Seppia, C., Ghione, S., Tonlorenzi, D., Brunelli, M., et al. (2013). Persistent effects after trigeminal nerve proprioceptive stimulation by mandibular extension on rat blood pressure, heart rate and pial microcirculation. *Arch. Ital. Biol.* 151, 11–23. doi: 10.4449/aib.v151i1.1470

Lapi, D., Federighi, G., Fantozzi, M. P., Del Seppia, C., Ghione, S., Colantuoni, A., et al. (2014b). Trigeminocardiac reflex by mandibular extension on rat pial microcirculation: role of nitric oxide. *PLoS ONE* 12:e115767. doi: 10.1371/journal.pone.0115767

Lapi, D., Varanini, M., Gheser, F., Ghione, S., Del Seppia, C., Scuri, R., et al. (2014a). "Effects of mandibular extension on low-frequency components," in *8th Conference of the European Study Group on Cardiovascular Oscillations ESGCO Rat Pial Arteriolar Rhythmic Diameter Changes* (Naples).

Loewinger, J., Cohen, M., and Levi, E. (1987). Bradycardia during elevation of a zygomatic arch fracture. *J. Oral Maxillofac. Surg.* 45, 710–711. doi: 10.1016/0278-2391(87)90315-6

Schaller, B. (2004). Trigeminocardiac reflex. A clinical phenomenon or a new physiological entity. *J. Neurol.* 251, 658–665. doi: 10.1007/s00415-004-0458-4

Schaller, B. (2005). Trigemino-cardiac reflex during transsphenoidal surgery for pintuary adenomas. *Clin. Neurol. Neurosurg.* 107, 468–474. doi: 10.1016/j.clineuro.2004.12.004

Schaller, B. J. (2007). Trigeminocardiac reflex. *J. Neurosurg.* 107, 243–244. doi: 10.3171/JNS-07/07/0243

Schaller, B., Cornelius, J. F., Prabhakar, H., Koerbel, A., Gnanalingham, K., Sandu, N., et al. (2009a). The trigemino-cardiac reflex: an update of the current knowledge. *J. Neurosurg. Anesthesiol.* 21, 187–195. doi: 10.1097/ANA.0b013e3181a2bf22

Schaller, B., Filis, A., Sandu, N., and Buchfelder, M. (2009b). Letter to the Editor: peripheral trigemino-cardiac reflex. *Acta Neurochr.* 151:1727. doi: 10.1007/s00701-009-0390-6

Schaller, B. J., Weigel, D., Filis, A., and Buchfelder, M. (2007). Trigemino-cardiac reflex during transsphenoidal surgery for pituitary adenomas: methodological description of a prospective skull base study protocol. *Brain Res.* 1149, 69–75. doi: 10.1016/j.brainres.2005.08.060

Schaller, B., Probst, R., Strebel, S., and Gratzl, O. (1999). Trigeminocardiac reflex during surgery in the cerebellopontine angle. *J. Neurosurg.* 90, 215–220. doi: 10.3171/jns.1999.90.2.0215

Sires, B. S., Stanley, R. B. Jr., and Levine, L. M. (1998). Oculocardiac reflex caused by orbital floor trapdoor fracture: an indication for urgent repair. *Arch. Ophthalmol.* 116, 955–956.

Stefanovska, A., Bracic, M., and Kvernmo, H. D. (1999). Wavelet analysis of oscillations in the peripheral blood circulation measured by laser Doppler technique. *IEEE Trans. Biomed. Eng.* 46, 1230–1239. doi: 10.1109/10.790500

White, S. W., and McRitchie, R. J. (1973). Nasopharyngeal reflexes: integrative analysis of evoked respiratory and cardiovascular effects. *Aust. J. Exp. Biol. Med. Sci.* 51, 17–31. doi: 10.1038/icb.1973.2

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