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Chapter 5

The Trigeminocardiac Reflex — An Example of Reflexive Heart Rhythm Change

Tumul Chowdhury, Belachew Arasho, Nora Sandu, Cyrill Meuwly and Bernhard Schaller

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http://dx.doi.org/10.5772/60215

Abstract

The trigeminocardiac reflex (TCR) is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnoea or gastric hyper-motility during mechanical/thermal stimulation of any of the sensory branches of the trigeminal nerve. The risk factors that are already known for increasing the prevalence of the TCR include anatomical location, hypercapnia, hypoxemia, light general anaesthesia, age (more pronounced in children), the nature of the provoking stimulus (stimulus strength and duration) and different drugs. Already different potential confounders are also identified. This discussion about risk factors has its importance because of the substantial consequences for functional outcome after intraoperative TCR occurrence. But there remains still a substantial lack of thorough understanding of the TCR, the current treatment options for patients with TCR include a mostly empirical approach: (i) risk factor identification and modification; (ii) prophylactic measures of vital signs and (iii) administration of vagolytic agents or sympathomimetics. In this context, we have now created different thinking models so that we can preoperatively plan a skull base surgery procedure safely in relation to a potential occurrence of the TCR episodes. This chapter provides an overview of this unique reflex that presents a unique interaction between heart and brain. In addition, this also illustrates the mechanism of various cardiac rhythm changes related to the TCR.

Keywords: Atropine, trigeminocardiac reflex, oculocardiac reflex, skull base surgery, treatment, trigeminal nerve, study design, evidence

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1. Introduction

The fifth cranial nerve is the largest of all the cranial nerves and provides sensory supply to the face, scalp, sinus and mucosa of the nose and mouth as well as the dura mater of the middle, anterior and part of the posterior cranial fossa [1–3]. Stimulation of any of these sensory parts of trigeminal nerve has been shown to initiate the trigeminocardiac reflex (TCR) and also produce various cardiac arrhythmias besides other less life-threatening symptoms [1, 3, 4, 5]. Initially, this reflex has been studied in animals and is therefore known for more than a century [6–8], under the term of "trigemino-respiratory reflex" and now its revival as sudden infant death syndrome (SIDS). In the early 20th century, the TCR has gained much clinical and less experimental attention in the form of the oculocardiac reflex (OCR) which is the predominant cardiac response associated with the stimulation of the ophthalmic division of the trigeminal nerve during ocular surgeries [9, 10]. Then later, Schaller et al., for the first time, demonstrated that the TCR occurred with the stimulation of the intracranial portion of the trigeminal nerve as well [1]. In addition, Schaller and his group later sub-summarized all these reflexes under the term TCR [2, 11], what is now generally accepted. Since then, there have been extensive discussions about the reflex itself, about the prophylaxis or risk factors, about treatment and about the influence of the TCR on functional outcome when it occurs during the intracranial or the extra-cranial procedures. Schaller and his group could demonstrate the ubiquitary occurrence of this reflex in any skull base procedure during 20 last years.

The TCR also serves as an important interaction between brain and heart, and thus provides deeper understanding of mechanisms related to various cardiac changes related to various extra/intracranial surgeries [4, 12–16]. The TCR represents as a model for different other diseases like, for example, sudden infant death syndrome (SIDS). Therefore, this chapter highlights the various aspects of TCR including its definition, epidemiology, risk factors and management. Special consideration is given to illustrate the mechanism of various cardiac rhythm changes related to the TCR.

2. Definition and pathophysiology of the trigeminocardiac reflex

Since its first description in 1999, the TCR is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnoea or gastric hyper-motility during stimulation of any of the sensory branches of the trigeminal nerve [1]. The proposed underlying mechanism for the development of the TCR is that the sensory nerve endings of the trigeminal nerve send neuronal signals via the Gasserian ganglion to the sensory nucleus of the trigeminal nerve, forming the afferent pathway of the reflex arc [1, 2]. This afferent pathway continues along the short internuncial nerve fibres in the reticular formation of the pons to connect with the efferent pathway in the motor nucleus of the vagus nerve in the nucleus ambiguus (see Figure 1) [1]. Since this initial description, nearly all trigeminal innervated structures except Meckel's cave have been reported to lead to a TCR. Several lines of experimental evidence demonstrate that trigeminal induced cardiovascular reflexes could be excitatory evoked initially in the trigemi-

http://dx.doi.org/10.5772/60215

nal nucleus caudalis and subsequently in the parabrachial nucleus, the rostral ventrolateral medulla oblongata, the dorsal medullary reticular field and the paratrigeminal nucleus [3, 17, 18]. Even so several studies on cellular level were performed, the exact cellular mechanism remains still to be explored.

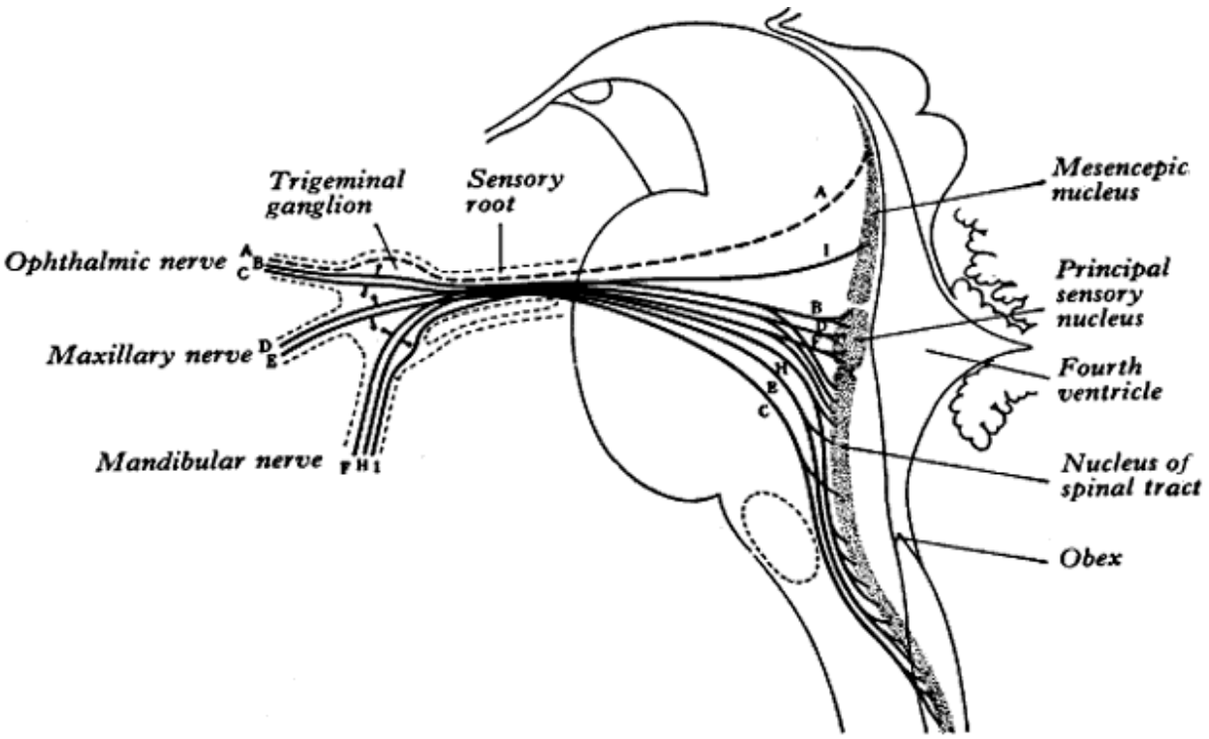


Figure 1. Trigeminal nerve with trigeminal ganglion and nuclei (from Warwick, R, Williams PL. Gray`s Anatomy, 35th ed., p 1001, Edinburgh, Churchill Livingstone, 1973)

According to the current knowledge, the TCR occurs during the peripheral and central manipulations of the trigeminal nerve as well as around Ganglion Gasseri manipulation. The OCR, which is an accepted peripheral sub-form of the TCR, has been reported in patients with ocular surgeries and consecutive trigeminal nerve manipulations since several decades [9, 10, 19]. After 1999, as Schaller et al., for the first time, reported the occurrence of the TCR in skull base and neurological surgeries, it was thought that OCR and TCR are both the same reflex [1]. The underlying cellular mechanism is not yet fully understood (see Figure 2), but is believed to be the same as the TCR reported earlier on in more detail during activation of the central or intracranial portions of the trigeminal nerve [2].

3. Epidemiology of the trigeminocardiac reflex

The TCR occurs with mechanical/thermal manipulation around any of the branches of the trigeminal nerve [9, 10, 19–23], with specific prevalence in specific anatomical locations [1]. The OCR being a sub-variant of the peripheral TCR is studied extensively earlier and was said

to occur in up to 67% after ophthalmic surgery [24]. Because of publication bias, the real prevalence may be substantially smaller, even the peripheral TCR has generally a higher prevalence than the central TCR. According to the senior author Schaller's experience, the central TCR occurs in up to 10–18% of the patients [1, 25–27]. In a retrospective time-series review of 125 patients operated for tumours of the cerebello-pontine angle, Schaller et al. noticed the TCR occurrence in 11%. [4] Three of these patients in this series developed asystole which lasted from 30 to 70 seconds [1]. In contrast to earlier studies on OCR, Schaller – for the first time – took into consideration both the heart rate and blood pressure and defined TCR as heart rate and mean arterial blood pressure (MABP) 20% lower than the baseline [1].

In another retrospective time-series study, Schaller also showed the TCR occurrence during microvascular decompression of the trigeminal nerve for trigeminal neuralgia [27]. In this review on 28 patients, the prevalence of TCR was up to 18% with the same definition used as in his prior above-mentioned study [27]. TCR was also reported during transsphenoidal surgery for pituitary adenoma [11, 26, 28]. Among 117 patients who underwent transsphenoidal surgery for pituitary adenoma, 10% developed a TCR during the surgical procedure [26]. Peripheral stimulation of the nasopharynx may also lead to (peripheral) TCR [11].

In several other neurosurgical procedures, there exists only case reports or small case series, so that a robust prevalence of TCR occurrence is not (yet) known.

4. Heart and the trigeminocardiac reflex

The TCR is a clinical phenomenon that reflects interactions of many organs to the brain [4, 12, 14, 19, 29–31]. Among all the organs, the connection between heart and brain is unique and presents a wide array of clinical manifestations when the TCR gets incited [16]. These clinical signs include drop in heart rate and blood pressure, asytole, ventricular tachycardia/fibrillation, ST-T wave changes and other forms of arrhythmias [4, 5, 12–16, 29, 31–65]. Stimulus especially in form of stretch has found to be the strongest inciting factor for the TCR [1]. However, mild stimulus may also results into TCR episodes [3, 18, 35]. Chowdhury et al. reported that mild stimulus in the form of skin closure could able to produce transient asystole and questioned about the severity of stimulus and TCR manifestation. In another report, Chowdhury et al. further suggested that various manifestations of TCR episodes (bradycardia, hypertension, asystole) as well as different subtypes of TCR (peripheral and central) could manifest in the same patient [4, 13]. Again, in this report, transient asystole manifested during the skin closure as well [4]. Author postulated that the different sympathetic outflow responses could be due to different depths of anaesthesia, which coupled with different forms of TCR stimulation probably contributed to different haemodynamic responses in the same patient and obscured the classical manifestation of TCR [3]. Strikingly, the cardiovascular changes of TCR phenomenon mainly reported due to acute stimulation (peri-operatively) of trigeminal nerve; however, Chowdhury and Schaller highlighted the first description of chronic form of TCR [40].

As highlighted in a review by Chowdhury et al., the other rare cardiac perturbation i.e. coronary spasm in neurosurgical patients may be the mere manifestation of TCR events [16].

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In this case series review, author found that in most of the neurosurgical conditions, dural stimulation provoked the ST-T wave changes, ventricular tachycardia and ventricular fibrillation [16]. The vagal mediated acetylcholine receptors have been also linked with the development of spasm [16]. Though majority of coronary spasm events were of transient nature (few minutes to few hours); however, very few of them also developed perioperative myocardial infarction.

5. Risk factors for occurrence of the trigeminocardiac reflex

Because of the still fragmented knowledge about the TCR and the consecutive limited therapeutic options, the risk factors gain increased importance. However, it is best known that such risk factors are not easy to proof in retrospective studies as they are predominantly available in TCR research. The risk factors already known to increase the incidence of TCR include (i) hypercapnia, (ii) hypoxemia, (iii) light general anaesthesia, (iv) age (more pronounced in children), (v) the nature of the provoking stimulus (stimulus strength and duration) and (vi) drugs. Recent systematic reviews, however, have identified several potential co-founders for these mentioned risk factors. Drugs known to increase the TCR include (i) potent narcotic agents (sufentanil and alfentanil) [66, 67], (ii) beta-blockers and (iii) calcium channel blockers [68]. Narcotics may augment vagal tone through their inhibitory action on the sympathetic nervous system [1, 69–71]. Beta-blockers reduce the sympathetic response of the heart and, by so doing, augment the vagal cardiac response resulting in bradycardia. Calcium channel blockers result in peripheral arterial smooth muscle relaxation and vasodilatation causing reduction in blood pressure. In patients undergoing trigeminal manipulations, this worsens the vagal effect that occurs in some patients. In previous publications about the TCR, the study design (mostly case control) may have led to different bias regarding the risk factors [39], such as recall bias and non-response bias to only mention two examples. From this point of view, a randomized controlled trial or a systematic review are requested to show best a cause-and-effect relationship for the risk factors.

In the recent years, it has more and more raised the question if the main search on risk factors is not a too linear thinking to overcome the complexity of the TCR. However, we think that risk factors are still an important key to better understand the TCR; even these risk factors have led to the development of the thinking model of TCR rather than to direct treatment consequences.

6. Clinical significance of the trigeminocardiac reflex and why it should be treated

Most authors recognized that the TCR is a transient, but potentially life-threatening response to any manipulation of the fifth cranial nerve subsiding with latency after cessation of the stimulus. But, in case of the development of severe bradycardia and asystole, the administration of peripheral muscarinic acetylcholine receptor blockage at the heart is warranted in

addition to cessation of the stimulus. Even so often mentioned, but still not understood from all: The vagal blockage potential of atropine is only insufficient for the prevention of hypotension or bradycardia.

Rath et al. reported a case of asystole occurring in a patient who was undergoing percutaneous retrogasserian glycerol rhizolysis for trigeminal neuralgia [72]. Immediately after the injection of anhydrous glycerol, the patient became unresponsive; the pulse became impalpable, blood pressure unrecordable, the ECG showed asystole and had a respiratory arrest. The patient regained consciousness and heart rate and blood pressure returned to normal after 30 seconds with oxygen and IV atropine [72]. Prabhakar et al. also reported a case of sudden asystole without prior bradycardia which occurred during surgery for cerebellopontine angle tumour [72]. This case was just managed by cessation of the manipulation without the administration of vagolytic agents [74]. Fayol et al. also reported a five-year-old boy who was operated for strabismus and possibly died due to OCR which developed on underlying myocarditis [74]. These cases demonstrate the (clinical) importance of the TCR which may range from mild bradycardia which responds to simple cessation of the stimulus to asystole and severe bradycardia requiring additional intervention with vagolytics. In some rare but serious cases, it may lead to death if not detected early and appropriate measures taken.

In addition, hypotension which occurs during the TCR may lead to myocardial and cerebral hypoperfusion/infarction in those who are at risk for these conditions. It has also been shown that the hypotension may lead to worse functional outcomes in hearing/vestibular function in patients operated for vestibular schwannoma compared to those who do not develop the reflex [25, 75]. In a prospective study of 100 patients after vestibular schwannoma surgery, Gharabaghi et al. found out that the occurrence of TCR was 11% [25]. With an overall hearing preservation of 47%, 11.1% of the patients in the TCR group and 51.4% of those in the non-TCR group experienced preserved hearing function postoperatively [25]. In addition, in cases involving larger tumours, an intraoperative TCR was associated with a significantly worse postoperative hearing function during vestibular schwannoma surgery suggesting that the hypotension following TCR is – in addition to the tumor size – a negative prognostic factor for hearing preservation in patients undergoing VS surgery [25]. In another study, Schaller et al. compared the occurrence and persistence of tinnitus in patients with and without TCR [76]. Among 36 patients operated for vestibular schwannoma, TCR occurred in 17% and influenced the occurrence of postoperative ipsilateral tinnitus: The overall incidence of postoperative ipsilateral tinnitus was 22%. A total of 60% patients in the TCR subgroup and only 17% of in the non-TCR subgroup experienced ipsilateral tinnitus postoperatively [76]. These studies show that there is a tendency for increased complication rates in patients who developed TCR compared to those without it, again stressing the importance of looking it carefully during neurosurgical and especially skull base surgical procedures.

7. Management of the trigeminocardiac reflex

The best and more effective treatment for TCR is still a matter of intensive debate [77–86]. It is beyond the scope of this manuscript to discuss all this in detail. Without any doubt, the application of atropine is not the only modality of treatment, based on cellular knowledge of

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the reflex and also based on the meanwhile extensive clinical experience. To the authors opinion, the first and the most important "management option" for the TCR is to be aware of its potential danger and to minimize any mechanical/thermal stimulation of the nerve during any interventional procedure in or around the skull base.

According to the empirical experience on the TCR, and according to the current level of evidence [87], we have summarized the current recommendation as follows [35]:

Risk factor identification and modification (*Evidence Grade D*)

Prophylactic treatment with either vagolytic agents or peripheral nerve blocks in case of peripheral manipulations of the trigeminal nerve (*Evidence Grade B–C*)

Careful cardiovascular monitoring during anaesthesia especially in those with risk factors for TCR (*Evidence Grade B–C*)

Treatment of the condition when it occurs (*Evidence Grade B–C*)

- cessation of the manipulation
- local anaesthetic infiltration or blockage of the nerve
- administration of vagolytic agents or adrenaline (peripher >> central >> Ganglion)

We can see that there is a lack of good evidence in the TCR, mostly based on the literature that is predominantly based on case reports and only seldom case-control studies. Additionally, this modest evidence is underlined by a substantial publication bias. As a consequence of this, the recommendations are more general as one might wish.

The risk of TCR, however, should be considered in any interventional procedure, especially at the skull base that takes place in trigeminally innervated structures. We have developed recently a thinking model that would give a preoperative idea about the risk of the TCR that can be expected in surgery in a specific neuroanatomical region [36]. If any mechanical stimulation to the trigeminal nerve is necessary, which is a rather "robust" nerve, it should be as gentle as possible. We have now different preoperative thinking models [36, 37] that should help the surgeon as well the anaesthetics to delimit the intraoperative occurrence of the TCR before operation and to perform adapted precautions. These manoeuvres should help to further decrease the incidence of the TCR.

If working in the vicinity of the trigeminal nerve or its branches, there should be an intensive communication between surgeon and anaesthesist. From our experience, this is perhaps one of the key factors of success. Continuous intraoperative haemodynamic monitoring has been shown to be an appropriate medium to interrupt any interventional manoeuvres immediately upon the first signs of occurrence of TCR. This technique has been proven to be sufficient to return to normal haemodynamic levels without the necessity of additional (anticholinergic) medication, if the cessation of stimulus was within a considerable time span before postoperative persistent neurological deficits occur [77, 78]. Following this empiric strategy, an uneventful further intraoperative and postoperative course may be achieved.

If controlled arterial hypotension is already preoperatively planned to be performed during the interventional procedure, the prophylaxis of TCR is better accomplished with local

anesthetic infiltration or block of the nerve(s) which convey afferent stimuli leading to the reflex. Shende et al. studied the efficacy of peribulbar block with bupivacaine in patients operated for retinal detachment [79]. They collected 60 patients who were randomly assigned to receive either bupivacaine or IV morphine and studied the incidence and severity of the OCR. Apart from significantly reducing the incidence of OCR (30% vs 70%), peribulbar bupivacaine also attenuated the severity of the reflex [79]. Gupta et al. studied the effect of peribulbar block in comparison to topical application of local anesthetic in children scheduled for strabismus surgery. They found out that the incidence and severity of OCR intraoperatively was significantly reduced in children who received a peribulbar block [80]. Misurya et al. studied the effectiveness of prophylactic intravenous atropine sulphate which blocks the peripheral muscarinic receptors at the heart and retrobulbar xylocaine hydrochloride, which blocks the conduction at ciliary ganglion on the afferent limb of OCR. In this study, both atropine and retrobulbar xylocaine reduced the rate of OCR to 10–20%. But, when both methods were used together, they were able to completely suppress the OCR [81].

If there is no contraindication to intravenous anticholinergics, atropine and/or glycopyrrolate IV may be used to partially prevent a TCR [82]. Hunsley et al. evaluated the efficacy of IV atropine and glycopyrrolate in the prevention of the OCR in children operated for strabismus. They tested different doses of the two drugs, glycopyrrolate 5 and 7.5 mg/kg and atropine 10 and 15 mg/kg. Overall, there is a reduction in the rate of bradycardia by 23.8–33.3% [83]. But these authors noticed that even higher doses of the two drugs, atropine 15mg/kg and glycopyrrolate 7.5mg/kg i.v., given 5 min before induction of anesthesia, are not sufficient to protect completely against the OCR in children. In a study done to evaluate the efficacy of IV or IM vagolytic agents (atropine and glycopyrrpolate) in children undergoing squint surgery, Mirakhur et al. evaluated them in a controlled study and found out that the administration of the anticholinergic agents in both the IV and the IM forms may decrease the occurrence of the OCR [84]. The overall frequency was approximately 40% (62 of 160 patients), but was 90% in those patients who did not receive anticholinergic drugs [84]. The authors concluded that the administration of anticholinergic drugs, even by the IM route, decreased the frequency, and glycopyrrolate 10 mg per kg being the most efficacious by this route [84]. As consequences of this literature and our own experience, the administration of anticholinergics has shown to be ineffective in completely preventing the TCR [73, 88]. The use of atropine is, nowadays, therefore questioned because cholinergic blockage reduces but does not totally prevent either bradycardia or hypotension in animals [85]. Another reason is that a trigeminal depressor response includes both the activation of vagal cardioinhibitory fibres and the inhibition of adrenergic vasoconstriction as demonstrated after electrical stimulation of the spinal trigeminal tract and trigeminal nuclear complex. In addition, atropine may cause serious cardiac arrhythmias itself, especially when halothane is the primary anaesthetic agent and hence the dose must be carefully chosen [86]. Prabhakar et al., for example, reported a 48-year-old female who developed severe bradycardia and hypotension during craniotomy for parietal convexity meningioma; she was unresponsive to atropine and successfully managed with epinephrine [89]. The action of adrenaline is to increase peripheral resistance via alpha-1 adrenoceptor vasoconstriction, so that blood is shunted to the body core, and the alpha-1 adrenoceptor response which is to increase cardiac rate and output [89]. This important case report under-

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scores the fact that TCR may be refractory to atropine and other vagolyticse and may rather need to be managed with epinephrine [89]. One the other hand, the personal experience with atropine is, besides its potential danger as described already earlier, that if given prophylactic in cases of risk for the occurrence of TCR it leads to a smaller change in TCR haemodynamic. In this context, the recently developed different thinking models help to better plan already preoperatively the procedure. This discussion about smaller haemodynamic changes has gained more and more importance during the last years, because of the functional outcome that is influenced by the TCR.

From our experience, the treatment of TCR deserves more attention in the daily practice. If a TCR is elicited, the underlying stimulus has to be stopped until the haemodynamic disturbances have been recovered to normal values. Any occurrence of the TCR corresponds to the intensity of the mechanical/thermal stimulation on the sensory part of the fifth nerve. From own and other clinical experience, abrupt and sustained traction is more likely to evoke the TCR than smooth and gentle manipulations [32–34, 78].

8. Recommendation from our practice

What makes us different from others? "Not a lot" is the answer. We use the same medication and the same procedures as in other large centres and as recommended here. These differences are only small and irrelevant to us. But we have highly standardized operative and anesthesiological processes [90–92]. This takes, for example, into consideration the relevant risk factors of TCR for skull base surgery. By this high standardization, we can reach also a high resilience of our processes, reflecting in the relative low prevalence of TCR compared to other centres [91, 93-95]. We have already previously summarized our recommendations [35] (Figure 2)

9. View to the future

The research on the TCR is now on a crossroad [39]. We have had a relative long phase in which case report and small case series have given substantial input to the development of the research on this topic. This research method has led to several biases in the TCR research: first in the prevalence and second in the risk factor, to mention only those both with that are mostly affected. This will be still needed in the future, of course, but we should now think to other research methods that lead to better evidence. In the first phase of TCR research, there were a lot of opinions that have led now to several really good systematic reviews that have created facts or at least trends. But starting from this newly created knowledge, there were now published several thinking models of the TCR to overcome on the one hand the complexity of information that is now available on this topic by generalizing and to make accurate forecast of risk for a specific operation. Such models helps us to better organize the information that is available and therefore make better decisions for our patients and adopt more effective treatment strategies. This new phase of TCR research has once again revolutionized the

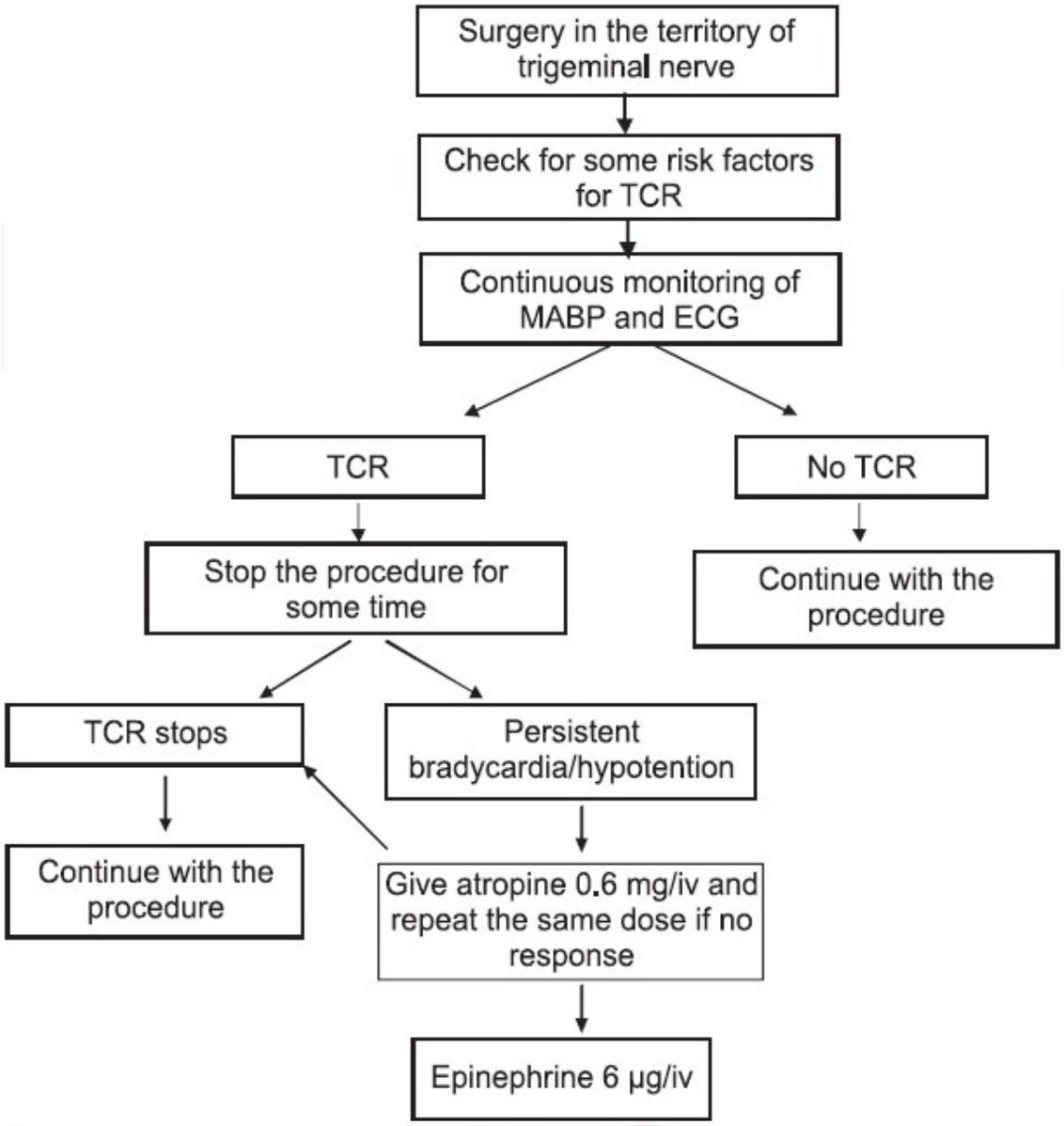


Figure 2. Treatment recommendation for trigeminocardiac reflex[35].

importance of the TCR: It is now possible to preoperatively have a really good risk stratification of the occurrence of the TCR.

These thinking model have certainly to be checked out and adapted when needed in the future [see for example 37], but we have now a good basis canalize and generalize our information and knowledge. This will lead that the TCR goes away from an interesting and important phenomenon to a real and important fact of the skull base surgery.

Following the increasing complexity of our today's hospitals, there is also the need to adapt the TCR prevalences to the new reality. It is and remains, without any doubt, important to uncover risk factors and to make root analysis of TCR occurrence. But in a next step, we have also to look on what is going well in the non-TCR cases and to uncover what makes

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the processes robust and resilient. This will be going up from a TCR-research I to a TCR-research II.

10. Conclusion

In the present paper, we illustrated the clinical relevance of the TCR on skull base surgery as well as neuroscience and discussed its management. Further clinical studies may help to describe the only partly understood reflex arc in more details on the one hand and to develop more precise prophylactic as well as intraoperative treatment options on the other hand. Such more expensive study designs will lead to better evidence in different aspects of the TCR research. But we have currently already good tools, like several thinking models that help, for example, to have already preoperatively an idea about the potential prevalence of TCR occurrence in a specific region of surgery and in specific patients. To additionally better understand the resilience of the non-TCR cases will further help to better understand the complexity of TCR occurrence and open the door for TCR research II. Anyway it will be exciting to follow the further research on this interesting and important topic of skull base surgery

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