

## Original Article

## Trigemino-cardiac reflex in neurosurgical practice: An observational prospective study

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Received: 26 May 13 Accepted: 16 July 13 Published: 18 September 13

**This article may be cited as:**

Etezadi F, Orandi AA, Orandi AH, Najafi A, Amirjamshidi A, Pourfakhr P, et al. Trigemino-cardiac reflex in neurosurgical practice: An observational prospective study. *Surg Neurol Int* 2013;4:116.

Available FREE in open access from: <http://www.surgicalneurologyint.com/text.asp?2013/4/1/116/118340>

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### Abstract

**Background:** Considering wide variations regarding the incidence of trigemino-cardiac reflex (TCR) during cranial neurosurgical procedures, and paucity of reliable data, we intended to design a prospective study to determine the incidence of TCR in patients undergoing standard general anesthesia for surgery of supra/intra-tentorial cranial and skull base lesions.

**Methods:** A total of 190 consecutive patients candidate for elective surgery of supra-tentorial, infra-tentorial, and skull base lesions were enrolled. All the patients were operated in the neurosurgical operating room of a university-affiliated teaching hospital. All surgeries were performed using sufficient depth of anesthesia achieved by titration of propofol–alfentanil mixture, adjusted according to target Cerebral State Index (CSI) values (40-60). All episodes of bradycardia and hypotension indicating the occurrence of TCR during the surgery (sudden decrease of more than 20% from the previous level) were recorded.

**Results:** Four patients, two female and two male, developed episodes of TCR during surgery (4/190; 2.1%). Three patients showed one episode of TCR just at the end of operation when the skin sutures were applied while CSI values were 70-77 and in the last case, when small tumor samples were taken from just beneath the lateral wall of the cavernous sinus TCR episode was seen while the CSI value was 51.

**Conclusion:** TCR is a rare phenomenon during brain surgeries when patient is anesthetized using standard techniques. Keeping the adequate depth of anesthesia using CSI monitoring method may be an advisable strategy during whole period of a neurosurgical procedure.

**Key Words:** Cavernous sinus, cerebral state index, depth of anesthesia, neurosurgery, skin suture, trigemino-cardiac reflex

**Access this article online****Website:**

[www.surgicalneurologyint.com](http://www.surgicalneurologyint.com)

**DOI:**

10.4103/2152-7806.118340

**Quick Response Code:**

### INTRODUCTION

The precise definition of trigemino-cardiac reflex (TCR)

was first suggested by a researcher in 1999 when he encountered a drop in mean arterial pressure (MAP) and heart rate (HR) during a skull base surgery procedure. He

defined the term of TCR as a drop in MAP and HR of more than 20% compared with the baseline values before the stimulus and coinciding with the manipulation around the trigeminal nerve endings.<sup>[9,24]</sup> Accordingly, TCR has been defined as any cardiac reflex triggered with stimulation of the trigeminal nerve anywhere throughout its central or peripheral course.<sup>[2]</sup> Those studying on oculo-cardiac reflex (OCR), regarded as an old subtype of TCR focusing on the HR only recalled it positive with a 10-20% decline in the HR coincident with the manipulation of the eye-related structures.<sup>[2,5,10,26]</sup>

The incidence of TCR in cranial surgeries has been reported in the range of 1.6-18%. It is noteworthy to mention that irrespective of two prospective studies in the literature, all of investigations regarding TCR had been performed either as a retrospective study or as case reports.<sup>[6,11,13,15,16,20,21,24,28]</sup> Considering wide variations regarding the incidence of this phenomenon during cranial neurosurgical procedures, and paucity of reliable data, we intended to design a prospective observational study to determine the true incidence of TCR in patients who were anesthetized with a standard technique for supra- and infra-tentorial cranial and skull base procedures.

## MATERIALS AND METHODS

We designed a prospective observational study to detect the incidence of TCR during cranial and skull base neurosurgical procedures, which was approved by the ethics committee of the university. Because this study was observational and noninvasive, only obtaining verbal consent from the patients was sufficed. A total of 190 consecutive patients with American Society of Anesthesiologists (ASA) grade I-III who were candidate for elective supra- and infra-tentorial craniotomy, trans-sphenoidal hypophysectomy and skull base surgery from September 2011 to November 2012 were enrolled. Patients who had any conductive heart blocking disease or any history of known autonomic system dysfunction, and those who underwent emergency craniotomy were excluded from the study. All episodes of bradycardia and hypotension during the surgery (sudden decrease of more than 20% from the previous level) coinciding with a simultaneous surgical manipulation in the territory of trigeminal nerve endings were regarded as TCR.<sup>[24]</sup> A uniform protocol was designed for treatment of all episodes of TCR as the following: The surgeon must be requested to withdraw the imposing stimulus and simultaneously a bolus dose of IV atropine (20 µg/kg) must be injected via a central venous line. If there were no acceptable changes after one minute, 100 µg of IV epinephrine must be injected. In case of resistant bradycardia/hypotension 1 mg of IV epinephrine would be the last choice. Depth of anesthesia was measured by a cerebral state index (CSI) monitor (Dan meter; Odense, Denmark) during the surgery.<sup>[1,4]</sup>

A CSI number in the range of 40-60 was regarded as an appropriate range for surgery. In the operating room, standard monitoring (electrocardiogram, pulse oximetry, invasive continuous blood pressure monitoring, capnography) was performed. All probable episodes of hypoxia ( $\text{SPO}_2 \leq 90\%$ ) or hypercarbia ( $\text{PaCO}_2 \geq 40$ ) or severe acidosis ( $\text{pH} \leq 7.2$ ) according to the pulse oximetry, capnography, and arterial blood gas (ABG) analysis results were recorded as well. General anesthesia was induced with a combination of IV midazolam (0.05 mg/kg), fentanyl (2 µg/kg), and propofol (2 mg/kg). Muscle relaxation was achieved using IV injection of atracurium (0.5 mg/kg). Anesthesia was maintained with infusing a mixture of propofol and alfentanil.<sup>[25]</sup> After surgeons main work with the lesion/removal of the lesion and at the hemostasis phase, the alfentanil was omitted from the mixture to avoid delayed patient awakening due to long context sensitive half-life of this narcotic. Thereafter, only propofol infusion was continued. Anesthesia method was the same for all patients except for titration of propofol-alfentanil mixture, which was adjusted according to target CSI values (40-60). For all patients and after induction of anesthesia, a radial arterial catheter was maintained and a central venous catheter was inserted in the right internal jugular vein. Age, sex, exact site of surgical manipulation, any previous drug or medical history, baseline hemodynamic parameters (systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, HR) before induction of anesthesia and at the moment just before TCR event were considered. The CSI number at the moment of TCR occurrence (for estimating the depth of anesthesia) was recorded. The medical therapy that was used for treatment of TCR episode was also recorded. Intraoperative fluid replacement therapy and blood products were administered based on ASA recommendations. The patients were ventilated on continuous mandatory ventilation mode. The ventilator setting was adjusted in order to keep the  $\text{PaCO}_2$  in the range of 30-35 mmHg based on the patients' ABG results, which was obtained every 30 minutes during anesthesia. All surgeries were performed by the same surgical team. Depth of anesthesia for all patients was kept in a range of 40-60 according to CSI monitor from the beginning of the surgery to the end of closure of the dural membrane. After commencement of skin suturing, the anesthetic drug infusion was tapered to prepare patients for awakening and extubation while the CSI monitoring continued up to the end of extubation process. Thus, it was anticipated that the CSI number would rise gradually that time (from 60-100). Patients were observed for detection of TCR until the end of detachment of head holder and wound dressing.

Standard monitoring continued in the recovery ward and all patients were transferred to the intensive care unit for the rest of their reanimation process.

## Statistical analysis

The primary outcome was determining the incidence of TCR during neurosurgical procedures and the secondary outcomes were determining the probable risk factors. Data were analyzed by SPSS version 19.1 software (Chicago, IL, USA). The incidence rate of TCR was obtained from the prospective study of Filis *et al.*<sup>[6]</sup> Then, this number was used for sample size calculation. Giving a 95% confidence level and an estimated incidence rate of 7.5%, a sample size of 190 subjects was calculated by loading the following formula:

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

$n$  = required sample size

$t$  = confidence level at 95%

$p$  = estimated incidence rate

$m$  = margin of error at 5% (standard value of 0.05)

We classified the pathologies to three main groups: (1) supra-tentorial gliomas or meningiomas, (2) infra-tentorial gliomas or meningiomas (in the skull base region and cerebellopontine angle), and (3) pituitary adenomas. Then, we calculated the Odds Ratio (OR) and Relative Risk (RR) for each group versus to the other one in the development of TCR.

## RESULTS

Data was collected from 190 patients who fulfilled the including criteria and underwent the neurosurgery. Demographics data of patients are shown in Table 1. Perioperative parameters are shown in Table 2. No episode of hypoxia or hypercarbia or acidosis was observed during the anesthesia period in all patients. Regarding the main sites of pathology, 172 patients had supra- or infra-tentorial lesions and 18 patients underwent trans-sphenoidal surgery for pituitary adenoma. In addition, different sites of the primary incisions are shown in Table 3. Three patients (two females and one male) presented only one episode of TCR at the end of operation when the skin suturing was being performed while the patients were presenting a CSI values between 70 and 77 (light anesthesia). The fourth episode of TCR occurred in a male who was deeply anesthetized (CSI = 51) for skull base surgery, while the surgeon was manipulating on just beneath the lateral wall of the cavernous sinus (near the central course of the trigeminal nerve). Detailed data of the cases are presented in Table 4. All four patients responded to injection of intravenous atropine (20 µg/kg) after warning the surgeons to avoid manipulation on the surgical field. All of patients were extubated successfully in the operating room and then transferred to recovery ward. In the recovery ward, they had an uneventful process (in terms of TCR) and finally transferred to the intensive care unit. Except for higher mean values of

**Table 1: Demographic variables of the patients**

	Mean ± SD	Max	Min
Age (years)	42.76 ± 15.73	77	2
Weight (kg)	70.21 ± 15.37	109	10
Sex	Male	Female	
Total number	75	115	

SD: Standard deviation

**Table 2: Base-line hemodynamic variables and peri-operative data of all patients**

Variables	Mean ± SD	Max	Min
Fluid intake (ml)	4840 ± 1550	10000	1600
Urine output (ml)	3330 ± 1520	8500	600
Mannitol (g)	74 ± 19	100	0
Base-line hemodynamic values			
SBP (mmHg)	130.51 ± 20.02	180	81
DBP (mmHg)	80.37 ± 11.72	109	49
MAP (mmHg)	97.08 ± 13.65	132.67	60.33
Baseline HR (beat/min)	80.69 ± 14.50	122	50

BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, HR: Heart rate, SD: Standard deviation

**Table 3: Distribution of the primary sites of surgical incision among patients**

Primary site of incision	TCR (+) (number)	TCR (-) (number)	Total (number)
Frontal	0	25	25
Parietal	0	16	16
Temporal	0	16	16
Occipital	1	11	12
Retro-sigmoid	0	2	2
Trans-nasal	1	17	18
Fronto-parietal	1	32	33
Fronto-temporal	0	22	22
Temporo-pareital	0	11	11
Parieto-occipital	0	2	2
Fronto-temporo-parietal	1	33	34
Total	4	186	190

TCR: Trigemino-cardiac reflex

CSI at the moment of TCR episode in the three of four TCR positive patients, (which is obviously the sign of a light anesthetic state) no important difference was found between the patients with and without TCR. Because of the low number of the cases with an episode of TCR, it was not statistically possible to perform a regression analysis for finding an association between probable risk factors and occurrence of TCR. But, we have run a statistical analysis and have calculated the OR and RR for all of predefined groups of the patients, which are presented in Table 5.

**Table 4: Medical history, demographic, and, peri-operative variables of the cases showed episodes of TCR**

Variables	Case no. 1	Case no. 2	Case no. 3	Case no. 4
Age (years)	56	14	45	26
Weight (kg)	70	45	93	67
Sex	Female	Female	Male	Male
Type of pathology	Supra-tentorial meningioma	Adenoma of pituitary	Supra-tentorial meningioma	Skull base meningioma
Site of operation	Fronto-temporal	Trans-nasal	Fronto-temporo-parietal	Occipital
Fluid intake (ml)	4000	3300	5300	4560
Urine output (ml)	1900	2100	2700	2500
Mannitol (g)	70	60	80	60
Operation time (min)	170	164	232	211
Anesthesia time (min)	205	214	275	246
Transfusion during surgery				
Packed cell (unit)	0	0	0	0
FFP (unit)	0	0	0	0
Platelet (unit)	0	0	0	0
Hemodynamic variables just before TCR episode				
SBP (mmHg)	102	89	92	87
DBP (mmHg)	64	55	54	64
MAP (mmHg)	83	72	66	85
HR (Beat/min)	68	85	74	68
Lowest BP and heart rate at TCR episode				
SBP (mmHg)	61	64	73	53
DBP (mmHg)	35	36	33	28
MAP (mmHg)	43	48	51	37
HR (beat/min)	41	34	32	18
CSI value at TCR episode	74	77	70	51
Manipulated tissue at the time of event				
Skin	+	+	+	-
Brain	-	-	-	+
Bone	-	-	-	-
Dura	-	-	-	-
Medical history	Mild hypertension	-	-	Nephrectomy due to renal cell carcinoma
Drug history	Captopril	-	-	-

FFP: Fresh frozen plasma, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, HR: Heart rate, CSI: Cerebral state index

**Table 5: The odds ratio and relative risk of three main groups of operations**

	Relative risk	Confidence interval	P value	Odds ratio	Confidence interval	P value
Supra-tentorial in compare to infra-tentorial surgery	7.31	(0.718-74.575)	0.054	7.95	(0.122-160.785)	0.054
Supra-tentorial in compare to trans-sphenoidal surgery	4.47	(0.426-46.917)	0.176	4.67	(0.074-92.864)	0.176

No one appeared to be significant

## DISCUSSION

This is the first observational prospective study designed for determining the incidence of TCR in neurosurgical patients who were controlled in terms of depth of anesthesia. The incidence of TCR in the current study was 2.1%. The result of this study is in concordance with the study of Precious and Skulsky.<sup>[16]</sup> Recently,

Yorgancilar *et al.* through a prospective study in the patients who underwent rhinoplasty procedures reported an 8.3% incidence of TCR.<sup>[25]</sup> Regrettably, they did not evaluate the depth of anesthesia and additionally, they defined a TCR episode as a sudden decrease of more than 10% in only one hemodynamic item (HR) of the patients (without considering decrease in blood pressure). This may be a reason for overestimating the incidence

of TCR in their study. Another prospective study that was reported by Filis *et al.* showed an incidence of 7.5% for TCR among transsphenoidal surgical patients.<sup>[6]</sup> The small sample size of that study and using no measure to evaluate adequate analgesia and hypnosis in patients under surgery were the main shortcomings. Schaller *et al.* retrospectively investigated 125 patients who underwent surgery in the cerebellopontine angle.<sup>[24]</sup> They reported an 11% incidence of TCR in those patients. However, their study was retrospective and also a confounding factor like unknown level of hypnosis or analgesia during the surgery casted doubt on their results. It must be considered that in addition to TCR, episodes of bradycardia and hypotension can occur in other situations like vasovagal reflex, which can be induced by the painful stimulations or hypovolemic or panic situations in any patients.<sup>[3,12,17]</sup> A horrible sound or a fearsome scene or even an unpleasant smell can frighten an awaken patient and provoke a vaso-vagal reflex during a surgical procedure while the surgeon is operating on the territory of trigeminal nerve. In this situation, how can we differentiate between an episode of vaso-vagal reflex and a TCR? Schaller reported a case series of 28 patients who underwent micro vascular trigeminal decompression because of trigeminal neuralgia in which they observed a high incidence of TCR (18%).<sup>[20]</sup> The reason for such a high rate of TCR occurrence might be surgical manipulation and direct stimulation of the trigeminal nerve. It is well known that anesthetic and narcotic drugs mainly exert their effects at the level of sensory receptor within the spinal cord and sometimes at the level of brain cortex. Thus, transfer of electrical impulses through the nerve fiber itself is spared during even deep level of general anesthesia. Therefore, the reason for observing one case of TCR in the situation of deep anesthesia (CSI = 51) may be direct stimulation of the nerve trunk. Many investigators through studies, which were performed on the OCR, found that several factors increased the risk of this reflex; hypercapnia, hypoxemia, age (more pronounced in children), light anesthesia, the stimulus frequency and intensity, and drugs such as narcotics, propofol, calcium channel, and beta blockers.<sup>[8,14,18,19,27]</sup> Because no independent study regarding to the risk factors of the so-called TCR has been conducted, we do not know if the risk factors of OCR is applicable to the so-called TCR or not? Accordingly, because all subtypes of TCR are mediated by the different branches of a single nerve, we can assume so. In this study, we infused a mixture of propofol and alfentanil for maintaining the anesthesia. But, in spite of prescribing propofol (100-150 µg/kg/min) and a potent rapid-acting opioid such as alfentanil (0.2-0.4 µg/kg/min) we observed only one episode of TCR (because of direct nerve manipulation) while adequate level of anesthesia was kept by using CSI monitoring. In contrast, three episodes of TCR (out of four) occurred

when the propofol infusion had already been tapered, and alfentanil infusion had already been stopped. This observation must attract our attention to this fact that keeping the patient in a deep level of anesthesia may prevent a TCR episode, even if the patient is prone to bradycardia because of using an infusion of alfentanil/propofol. This observation may support the study of Yi and Jee.<sup>[27]</sup> They suggested that OCR is relevant to the depth of anesthesia. They concluded that when they kept the bispectral index values at about 40-50 in pediatric patients undergoing general anesthesia for strabismus surgery (they kept deep level of anesthesia); it decreased the incidence of OCR.

Even though, some investigators propose that the TCR is phylogenetically, just like 'diving reflex' in birds and amphibians and may have a protective role in human being, Occasional reports of death due to TCR, create a major concern regarding this life threatening phenomenon in mind.<sup>[7,14,22,23]</sup> Blunting the autonomic reflexes might be considered as one of the main issues in a balanced and safe anesthesia. Thus, just like the other types of autonomic reflexes that may be hazardous and should be controlled during general anesthesia, the TCR may also have a deleterious effect on the safety of the patient and must be meticulously taken care of during cranial and skull base surgeries.

## CONCLUSION

According to this study, it is found that the incidence of so-called TCR during cranial and skull base surgery can be very low while performing a standard neuro-anesthesia practice. The number of TCR events in our study was not sufficient enough to perform an advanced statistical analysis; we would like to suggest that all patients who undergo craniofacial surgeries are better to be anesthetized deeply. This strategy may lessen the incidence of TCR to the least and reduce its danger. This suggestion may contradict with the current growing concept of the craniotomy in patients who are not deeply anesthetized electively.

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