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Anesthetic Influence on Occurrence and Treatment of the Trigemino-Cardiac Reflex

A Systematic Literature Review

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Abstract: Trigeminocardiac reflex (TCR) is defined as sudden onset of parasympathetic dysrhythmia including hypotension, apnea, and gastric hypermotility during stimulation of any branches of the trigeminal nerve. Previous publications imply a relation between TCR and depth of anesthesia. To gain more detailed insights into this hypothesis, we performed a systematic literature review.

Literature about occurrence of TCR was systematically identified through searching in Cochrane Central Register of Controlled Trials (CENTRAL), PubMed (MEDLINE), EMBASE (Ovid SP), and the Institute for Scientific Information (ISI Web of Sciences) databases until June 2013, as well as reference lists of articles for risk calculation. In this study, TCR was defined as drop in mean arterial blood pressure and heart rate, both >20% to baseline. We calculated intraoperative cerebral state index (CSI) of each TCR-case using a newly developed method. These data were further divided into 3 subgroups: CSI <40 (deep anesthesia), CSI 40–60 (regular anesthesia), and CSI >60 (slight anesthesia).

Including 45 studies with 910 patients, 140 (15%) presented with TCR, and 770 (85%) without TCR during operation. TCR occurrence showed a 1.2-fold higher pooled risk slighter anesthesia (CSI <40: 13%, at CSI 40–60: 21%, and at CSI >60: 27%) compared with deeper anesthesia. In addition, we could discover a 1.3-fold higher pooled risk of higher MABP drop with a strong negative correlation ($r = -0.935$; $r^2 = 0.89$) and a 4.5-fold higher pooled risk of asystole during TCR under slight anesthesia compared with deeper anesthesia.

Our work is the first systematic review about TCR and demonstrates clear evidence for TCR occurrence and a more severe course of the TCR in slight anesthesia underlying the importance of skills in anesthesia management during skull base surgery. Furthermore, we have introduced a new standard method to calculate the depth of anesthesia.

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Abbreviations: CSI = cerebral state index, GG = ganglion Gasseri, MABP = mean arterial blood pressure, OCR = oculocardiac reflex, TCR = trigeminocardiac reflex.

INTRODUCTION

Trigeminocardiac reflex (TCR) is a well-established brainstem reflex that is commonly reported during different skull-base interventions[1–4] and is defined as the sudden onset of parasympathetic dysrhythmia including bradycardia and asystole, sympathetic hypotension, apnea as well as gastric hypermotility during the stimulation of any of the sensory branches of the fifth cranial (trigeminal) nerve.[1] TCR was first described clinically in humans by the senior author in 1999;[1] thereafter it has become a generally accepted phenomenon in nearly all the disciplines involved in surgical neurosciences.[5–14] In the recent past, Schaller and colleagues have further explored the differentiation of TCR into peripheral,[5,15] central,[1,8] and ganglion Gasseri (GG) TCR subtypes;[16] each with differential clinical behavior as well.[17] In this context, the influence of intraoperative occurrence of TCR on clinical outcome has developed more and more interest,[7,18,19] so that the questions about intraoperative prophylaxis or prevention of the TCR were increasingly raised.[4,20,21]

In the recent past, the influence of different anesthetic drugs on the TCR was evaluated by several experimental researchers. Therefore, we know that the TCR is less often by using sevoflurane than halothane[22] or ketamine; TCRs is less often seen rarer when using using propofol.[23,24] In addition, the excitatory effect of fast acting opioids on the TCR has also already been shown by Arnolds and colleagues as well as others.[25–27] Next to these gained facts in experimental research, we do not know more details about the influence of anesthesia on the occurrence of the TCR. Only few clinical articles have suggested that there could be existence of anesthetic drugs as well as depth-related influences on the occurrence of TCR episodes.[1,28] However, literature does not provide substantial evidences on this issue. In this present work, we, therefore, have tried to find out evidence related to anesthesia-dependent influences on the intraoperative occurrence and treatment of the TCR in different surgical procedures during a 15-year period. The objectives of this literature review were to compare the risk of the intraoperative occurrence of the TCR, the evidence of treatment of the TCR, and the risk of intraoperative asystole caused by the TCR. In all these three outcome parameters, we compared different depths of anesthesia and related anesthetic drugs.

MATERIALS AND METHODS

Data Source and Searches

We have performed a comprehensive literature research in Cochrane Central Register of Controlled Trials (CENTRAL),

PubMed (MEDLINE), EMBASE (Ovid SP), and the Institute for Scientific Information (ISI Web of Sciences) databases until 6/2013 for the terms ''Trigeminocardiac reflex'', ''Anesthesia and Trigeminocardiac reflex'', ''Trigeminal depressor response'', ''Asystole/Bradycardia and Neurosurgery'', and ''Oculocardiac reflex''. We have carried out all researches for these key words from January 1999 to June 30, 2013. In addition, reference lists of all included articles were reviewed to identify additional relevant articles. The literature research was done using the commercial reference management software EndNote (EndNote X601, Thomson Reuters).

Definition of TCR

We defined the occurrence of a TCR episode for the clinical purpose of this study as *hypotension*, a drop in mean arterial blood pressure (MABP) of 20% or more and *bradycardia*, a drop of heart rate of 20% or more from the baseline, and/or asystole.[1] The occurrence must be preceded with definitive stimuli including physical, chemical or electrical manipulation at or near the vicinity of trigeminal nerve (peripheral or the central part).[1]

The central TCR is defined as an origin of the TCR cranial to GG, the peripheral TCR, as distal to GG, and a TCR of the GG as a direct stimulation on the trigeminal ganglion.[16]

Inclusion Criteria

The following inclusion criteria for the review were used: adult aged >18 years undergoing elective or emergent surgery under general, regional or local anesthesia, or a combination; articles written in English, German, or French; articles published after the first description of a manifested TCR in surgery of the cerebellopontine angle by the senior author in 1999[1]; the TCR fulfills our definition of a TCR according to the definition made earlier the senior author in 1999[1]; and the TCR is during and not after operation. In addition to the inclusion criteria, it was necessary that the included article reports about at least 1 TCR-case.

We considered all types of studies [randomized controlled studies, cohort studies, case series, case reports] in all types of publications [systematic reviews, articles, letters, comments], as long as they reported about at least 1 case of TCR and fulfilled the inclusion criteria. If there was no link to a full text version available through the various search engines: we tried to contact the author; if not successful, we excluded the article. Papers related to animal experiments and duplicated data were not included in this review.

Types of Interventions

This review has considered any intervention in the skull base leading to a TCR occurrence. Consideration is given only to interventions that lead to a TCR *during* the intervention itself. Studies reporting multiple co-interventions were not eligible for inclusion, unless the same co-interventions were used in both subgroups.

Data Extraction and Quality Assessment

For data extraction, 2 independent reviewers (C.M./M.R.) selected all titles/abstract. Articles that could not be excluded on the basis of title and/or abstracts were assessed for defined eligibility criteria in full text. If there was no agreement, the articles were read and checked for inclusion by a third reviewer (B.S.) independently, and the decision was made after thorough discussion according to PRISMA guidelines (Figure 1). The selection of the included trials or case series was performed according to the data included in the summary. If we were not able to confirm all including criteria through the summery, the whole publication was evaluated. The following data were extracted from the included studies: publication date, episodes of TCR/Non-TCR, gender, detailed drop of MABP, age, localization of the manipulation (central vs. peripheral), prophylactic drugs used to prevent TCR episodes, treatment of TCR episodes, and used anesthetic drugs. Every case report was checked for double publication.

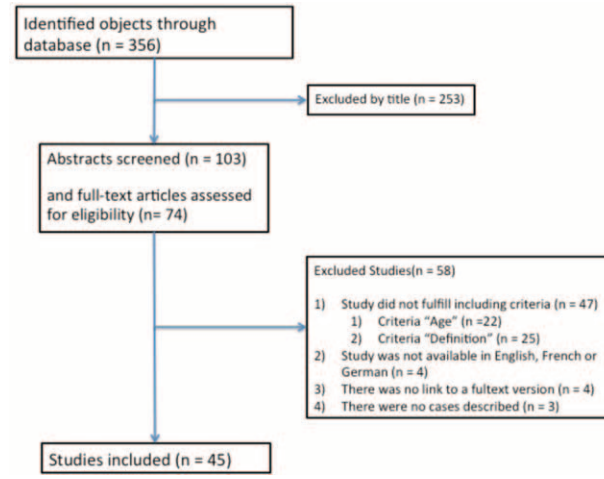

FIGURE 1. Flowchart of study design according to PRISMA.

Risk of Bias

We analyzed the risk of different bias in our study and identified as most relevant biases for our systematic literature review. The data were evaluated for biases using the ''Cochrane Handbook for Systematic Reviews of Intervention''.[29]

Data Synthesis and Analysis

Collected data and results in the studies were also checked by 2 reviewers (C.M./M.R.) independently for finding differences in the extracted data, if any. According to the above-mentioned definition of TCR, we divided the patients into 2 groups: TCR group and non-TCR group.

For reported anesthesia protocol, we calculated 'the assumed depth of anesthesia'. For this, we scaled a mean regular deep anesthesia at the beginning of the narcosis at a cerebral state index (CSI) between 40 and 60, which is expected in anesthesia induced by propofol 2 to 3 $mg\,kg^{-1}$ and fentanyl 3 to 5 $\mu g\,kg^{-1}$.[30] In less drug use then the defined amount was expected to result in light plane of anesthesia and a CSI >60; more drug use in as a CSI <40. We also assessed whether the maintenance of the anesthesia was performed by intravenous or volatile drugs. If intravenous drugs, as propofol and fentanyl (or its derivates), were given during the maintenance, we used this scale in these reported cases to calculate the CSI during the TCR episode. If volatile agents were used for the maintenance, we assumed an adequate depth of anesthesia (CSI 40–60) at an end-tidal concentration of minimum 0.6 to 1.2% for isoflurane, 0.35 to 0.7% for halothane, and 0.9 to 1.8% for sevoflurane.[31–32] A mean end-tidal concentration of <0.6% for isoflurane, 0.35% and 0.9% for halothane and sevoflurane,

TABLE 1. CSI in the TCR/Non-TCR Group

CSI depth	TCR (%)	Non-TCR	Total	RR (95% CI)
CSI <40	13 (13%)	88	101	0.81 (0.48–1.39)
CSI 40–60	48 (21%)	185	233	1.51 (1.10–2.07)
CSI >60	11 (27%)	30	41	0.66 (0.48–0.89)
NA	68	467	535	
Total	140	770	910	

CI = confidence interval, CSI = cerebral state index, NA = not available, RR = relative risk, TCR = trigeminocardiac reflex.

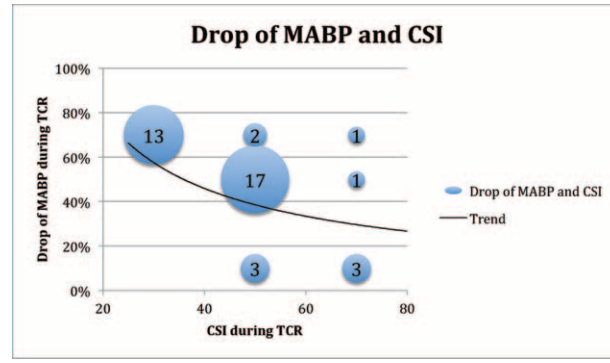

FIGURE 2. The detailed drop of MABP in the 3 CSI-groups.

respectively, was assumed as an CSI >60 and a concentration of more than 1.2%, 0.7%, and 0.9% for isoflurane, halothane, and sevoflurane was assumed as an CSI <40.

We divided both the TCR and non-TCR group into the following 3 subgroups according to the calculated CSI: CSI <40 (deep anesthesia); CSI 40–60 (regular anesthesia); and CSI >60 (light plane of anesthesia). For each group we calculated: the incidence of occurrence of the TCR (Table 1), the detailed drop of MABP during the TCR episode (Figure 2), the use of atropine as the management of the occurrence of a TCR, and the incidence of asystole which was defined as a flat line in the electrocardiography (Table 2).

Statistical Analysis

All the statistical analyses were performed using statistical software (JMP, SAS Institute Inc., Cary, NC; USA) on a commercially available computer. Data were tested for normality using the D'Agostino and Person omnibus normality test. Data normally distributed are represented by mean (SD).

Dichotomous data were analyzed using risk ratios with 95% confidence intervals (CIs). For continuous data, there were used mean differences and 95% CIs.

We analyzed available data on an intention-to-treat basis.

Before obtaining pooled estimates of relative effects, we carried out a statistical heterogeneity analysis by assessing the value of the I^2 statistic, thereby estimating the percentage of total variance across studies is due to heterogeneity rather than to chance. We considered a value >30% as a sign of important heterogeneity, and, if present, we sought an obvious explanation for the heterogeneity by considering the design of the trials. We then proceeded to a meta-analysis only when the direction of effect was the same for all point estimates.

To compare 2 independent proportions, Fisher exact test was used. To compare more than 2 independent proportions, χ^2 test was used. The level of significance was set for both at a $P < 0.05$. Spearman's rank correlation coefficient was used to quantify a relationship between 2 or more variables; a 2-tailed P values <0.05 was considered statistically significant.

We used Der Simonian and Laird random-effects models meta-analysis of risk ratios in Rev Man 5.2 for dichotomous data and weighted mean differences for continuous data. Pooled estimates include a 95% CI.

For subgroup analysis, the CSI was not scaled as interval data because the method we developed to calculate the CSI only allows us to classify the depth of anesthesia as ordinal-scaled data. Therefore, Fisher exact test was used in all the analysis.

For detailed trend lines (Figure 2), the analysis was done by using the potential formula and values out of the collected data the prognosis were calculated by using, for both, R version 3.1.2 (Pumpkin Helmet).

Ethics

The analysis was performed as part of the Master Thesis by the first author, which was assessed by the ethics committee of the University Basel.

RESULTS

Overall, 45 studies harboring 140 patients for the TCR subgroup and 770 patients for the non-TCR subgroup, respectively, met the inclusion criteria for the systematic review (Figure 1 and Table 3). The I^2, as sign of heterogeneity, was 96% (TCR subgroup) and 97% (non-TCR subgroup). There were non-significant differences in the patients' age, gender, surgical interventions, and previous arrhythmias between the TCR and non-TCR subgroup (Table 2). But there was a significant more frequent previous myocardial infarction in the TCR compared with the non-TCR subgroup ($P = 0.03$; see Table 2).

TABLE 2. Occurrence of Asystole in Relation to the Depth of Anesthesia in TCR

Asystole	CSI <40	CSI 40–60	CSI >60	Total	RR (CI 95%)
Number (%)	13 (18%)	48 (67%)	11 (15%)	72	
Yes	0	5 (20%)	3 (30%)	8	0.93 (0.59–1.63)
No	13 (100%)	20 (80%)	7 (70%)	40	3 (0.99–9.05)
NA	0	23	1	24	
Total	13	48	11	72	

CI = confidence interval, CSI = cerebral state index, NA = not available, n.s. = not significant, RR = relative risk, TCR = trigeminocardiac reflex.

TABLE 3. Patient's Characteristics in the TCR and Non-TCR Group

Characteristic	TCR Group	Non-TCR Group	Total	*P*
No. of patients	140 (15.4%)	770 (84.6%)	910	...
Mean age	52 (18–76)	54 (NA)	NA	n.s.
Gender				
Women	67	229	296	n.s.
Men	49	238	287	
NA	24	303		
Surgical interventions				
Neurosurgery	102	731	833	
ORL	7	0	7	
Ophthalmology	31	39	70	
Classification				
Central	95	708	803	
Peripheral	35	39	74	
GG	7	23	30	
NA	3	0	3	
Cardiac diseases				
Previous arrhythmias	7	39	46	n.s
Previous MCI	3	0	3	$P = 0.03$

GG = ganglion Gasseri, MCI = myocardial infarction, NA = not available, n.s. = not significant, TCR = trigeminocardiac reflex.

Among TCR group, 95 (68%) had a central TCR, 35 (25%) patients a peripheral TCR and 7 patients (5%) a TCR induced by direct stimulation on the GG. In 3 patients (2%), we were not able to categorize the TCR.

For anesthesia protocol, propofol was used as the commonest anesthetic agent for the maintenance of anesthesia in 94 TCR cases (67%) and the other anesthetics (isoflurane and sevoflurane) in 46 (33%) TCR cases ($P = <0.0001$) (Table 4).

For the depth of anesthesia objective criteria, we could categorize the CSI in 72 (51%) out of 140 patients in the TCR subgroup and in 303 (39%) out of 770 patients in the non-TCR subgroup, respectively. The I^2 was 36% for both subgroups. In 13 (18%) out of these 72 TCR subgroup patients, the maintenance of the anesthesia was performed with inhalative agents (isoflurane) while in the remaining 59 (82%) patients the maintenance was performed with intravenous agents (propofol or opioids). In 12 of 13 cases (92%) of the ''volatile agents'' group, isoflurane was the applied inhalative drug, whereas in only 1 case (8%) sevoflurane was used. In this collective, there was a 1.2-fold higher pooled risk that TCR occurs in slight anesthesia (CSI >60) than in deeper anesthesia) (Table 1).

In CSI >60, 41 patients (11%) had maintenance of anesthesia with propofol or volatile agents compared with 233 patients (62%) in case of CSI 40–60 and compared with 101 patients (27%) in case of CSI <40; 27% (11 patients) in CSI >60 subgroup, 21% (48 patients) in CSI 40–60 subgroup and 12.8% in CSI <40 subgroup presented a TCR event ($P < 0.0001$).

Next, we analyzed the detailed changes on MABP and compared the minimum value with the baseline during the TCR episode. Detailed data were available for 40 included patients. The CSI <40 group contained 13 patients with a minimal drop of MABP to 60–80% compared with baseline (RR: 10.15; CI (95%): 2.6–39.1) and there were no patients with a drop of >40%. The CSI 40–60 group contained 2 (9%) patients with a minimal drop of MABP to 80–60% (RR: 0.16; CI (95%): 0.04–0.60), 17 (77.3%) patients with a drop of MABP to 40–60% (RR: 5.01; CI (95%): 2.23–11–25), and 3 (13.7%) patients with a drop of MABP under 20% (RR: 0.78; CI (95%): 0.31–1.95). In the group with slight anesthesia (CSI >60), we included 1 (20%) patient with a drop of MABP to 60–80% (RR: 0.40; CI (95%) 0.040–3.32), 1 (20%) patient with a drop of MABP to 40–60% (RR: 0.43; CI (95%): 0.05–3.60), and 3 (60%) patients with a drop of MABP of over 80% (RR: 7.5; CI (95%):1.5–36.94). There was 1.3-fold higher pooled risk of higher MABP drop in slight anesthesia (CSI >60) compared with deeper anesthesia showing a strong negative correlation ($r = -0.935$, $r^2 = 0.89$) (Figure 2).

Regarding the use of atropine in the TCR subgroup, there is a significant increased frequent use of atropine during light anesthesia (CSI >60) compared with regular anesthesia (CSI 40–60) ($P = 0.024$). The CSI <40 subgroup does not contain enough data to analyze (only 1 case with use of atropine).

TABLE 4. The Anesthetic Protocol Used to Calculate the CSI Out of Drug Use for Anesthesia

	Propofol and Fentanyl	ETC Isoflurane (%)	ETC Halothane (%)	ETC Sevoflurane (%)
CSI < 40	Higher dosage	<0.6	>0.7	>1.8
CSI 40–60	Propofol 2–3 $mg\,kg^{-1}$ and fentanyl 3–5 $\mu g\,kg^{-1}$	0.6–1.2	0.35–0.7	0.9–1.8
CSI >60	Lower dosage	>1.2	<0.35	<0.9

CSI = cerebral state index, ETC = end-tidal concentration.

Again in the overall collective, we could find a 4.5-fold higher pooled risk of asystole in the light anesthesia subgroup (CSI >60) of the TCR subgroup compared with the other CSI subgroups (Table 2).

DISCUSSION

TCR and related risk factors have gained much interest during recent years. In this work, we have analyzed, for the first time, the relation between light anesthesia (CSI >60) and TCR occurrence highlight a strong association. As well we found a higher pooled risk for slight anesthesia for stronger MABP drop during TCR and for occurrence of asystole during TCR suggesting a more severe reflex variant under these conditions. In the context of differences in anesthesia management, we further have analyzed the use of atropine in TCR management and have also found a more significant use

Possible Mechanisms

It has been already shown that the different anesthetic agents have different effects on trigeminal nucleus neurons.[33–35] In this context, the best-known anesthetic risk factor for the TCR in children is fast acting opioids such as fentanyl.[25–27] Unfortunately, the effect of propofol, an anesthetic that is currently often used in skull base anesthesia, in respect to the TCR is not fully evaluated yet. So far, Mendelowitz and colleagues analyzed the excitatory postsynaptic potential of the cardiovascular neurons in the nucleus ambiguous after application of propofol and noticed no change.[35] Anyhow, our present analyses describe a trend towards higher anesthetic doses having an inhibitory effect on the TCR, depending on the administered dosage. The prevalence of TCR in the CSI >60 subgroup (light anesthesia) was consecutively higher than in the CSI 40–60 (regular depth of anesthesia) and CSI <40 subgroups (deeper anesthesia than regular). Unfortunately, there was no awake brain surgery patient included into this study that would further underline our hypothesis. Furthermore, there is a strong trend for light anesthesia to be a risk factor for a more intense (asystolia) reflex as compared with a regular depth of anesthesia underlying additionally the influence of light anesthesia to the autonomous nerve system.

We can also describe a significant correlation for propofol to influence the occurrence and intensity of the TCR. Both trends together strongly imply that propofol has also an inhibitory effect of either the afferent trigeminal neurons or the efferent cardiac vagal neurons, or both in clinical conditions as described earlier experimentally.[35]

The inhibitory effect of atropine on TCR occurrence is already well known, as well as the fact, that atropine does not totally prevent TCR.[21,36–37] In our review, we were not able to describe any differences in incidence of atropine use related to depth of anesthesia. It is therefore questionable if atropine is the best treatment for the TCR because not all TCR cases can be fully stopped with the atropine application in humans (only muscarinic receptor antagonist)[21,36–37] and atropine itself can cause severe arrhythmia[1,38] or other side effects especially when admitted in ocular operations (optic nerve damage, retro bulbar hemorrhage or stimulation of the oculocardiac reflex (OCR) by the retrobulbar block itself). We therefore recommend, based on our study here and on our previous study[4] reflecting our personal experience, that the treatment of the *central* TCR either with stop of surgeon's manipulation or, in heavy and repetitive cases, with the use of epinephrine to stabilize the cardiovascular balance. The number of in this systematic review included cases treated with epinephrine was too small to make a generalizable conclusion. For the *peripheral* TCR, there are currently not sufficient data with a good quality available to make any serious recommendation. But, especially for ocular surgeries in children, preventive use of atropine (retrobulbar block) can be necessary.

Cardiac Diseases

As the predominant number of studies included into this systematic review were of retrospective design any relation between previous cardiac diseases and subtypes of anesthetic used was not possible. Even the often mentioned American Society of Anesthesiologists physical status classification system excludes very severe previous cardiac diseases.

Prevention of the TCR

In general, preventive use of atropine is highly disputable because of the prior mentioned reasons. Until we better understand the whole TCR physiology, it is therefore recommended to rather reduce the proposed TCR risk factors as also seen in this work. The prophylactic reduction of known pharmacological risk factors before surgery and the decrease of hypercarbia as well as hypoxia during surgery (eg, sufficient application of anesthetics) is therefore currently the best way to decrease TCR occurrence. Another factor represents certainly the awareness and capability of the surgeon to perform the (micro)surgical preparation with smooth and slow tractions around the trigeminal nerve or 1 of its branches.[39]

Strengths and Weakness of the Study

In our present review, we describe – for the first time – a systematic literature research about the depth of anesthesia being a risk factor for the TCR occurrence. The fact, that we defined strict inclusion criteria helps our result to be more valuable as discussed in detail before[1]. By help of such a strict methodological approach, our research has less confounder (such as different physiology in younger patients and unsure manifestation of TCR with wider definition of TCR) what results in an overall more valuable result. Although we had to exclude many patients, we still included 140 patients with a proven TCR (and 770 patients in the non-TCR-group), representing the study including the largest number of TCR patients ever done, so that our results are supported as best as possible.

We are aware, that it is not possible to prove a significant pooled risk difference with such a huge number of case reports as included in this study. This fact gives place to a certain publication bias: In our study, 39 out of 140 included patients were extracted out of case reports, so that there is certainly an over-representation of TCR compared to non-TCR patients, even the I^2 value was sufficient. We tried to exclude all case reports[36,38,40–71] and to analyze the pooled risk difference of TCR in relation to the depth of anesthesia. But the data resulted were too small for a detailed analysis (only 66 cases with calculated CSI remained; 12 with CSI <40, 43 with CSI 40–60, and 6 with CSI >60). It is not usual that the precise depth of anesthesia during a regular surgery is reported in clinical studies. Because of the retrospective manner of our review, we had therefore to develop an instrument to calculate the CSI during the TCR to maintain data quality. By our chosen methodological approach, we therefore tried retrospectively to evaluate the CSI as exact as possible with the extracted data. But we have to keep in mind, that the calculated CSI is only an estimated number and a reflection of a relative method to

measure depth of anesthesia, especially related to previous research about the correlation between drug dose (for propofol) or end-tidal-concentration (for volatile agents) and the resulted CSI. The real CSI varies in each patient and is dependent on different variables (like, eg, age, weight, anesthetic clearance, kidney function, previous diseases) that not all could be considered in the systematic review of predominantly retrospective studies.[72] Such patient's and study characteristics, with a large number of observational studies, are possible confounders for our review and could be excluded by sub-group-analyses. Unfortunately, the included papers do not contain enough information for such detailed analyses. The strong correlation between bispectral index and CSI has also been shown in previous studies for intravenous or volatile agents.[30,73] For all these factors, the developed method seems to be a reasonable way to analyze TCR events related to the depth of anesthesia. To overcome such methodological bias and to be sure that the data quality is sufficient, we have done a methodological triangulation by examining the use of atropine confirming our results. Similarly, our gained results are generalizable.

Other generally accepted risk factors for TCR such as hypercapnia, hypoxemia, and drugs (eg, potent narcotics, beta-blockers, calcium channel blockers)[17,74–77] could be possible confounders for such an analysis. We tried to extract data about these risk factors, but most of the included articles did not precisely mention these factors. Again, the triangulation let us to be sure that the light anesthesia is a strong an independent risk factor.

For our work, we set strict inclusion criteria as defined earlier by Schaller and colleagues[1] leading to exclusion of a substantial part of the published TCR studies. We are therefore aware that our study has an inclusion criteria bias and that some important literature was excluded (47 studies including 5035 patients) because it did not fit our very strict inclusion criteria. Most of these described cases of the OCR, which is a TCR subtype harboring a much higher incidence (until 90% in ophthalmologic surgeries). Some of the excluded studies report for example about patients under 18 years old (22 studies including 4557 patients, again, most OCR reports), but these patients were excluded because there is expected a different TCR physiology in children. Others defined the TCR as a drop of MABP and HR of 10%, which is, from our point of view, not a clear TCR manifestation but rather physiological fluctuations during the operation (25 studies including 478 patients). Due to these strong criteria, we lost consecutively some statistical power.

Strengths and Weakness in Relations to Other Studies

During the last few years, there was an ongoing discussion about risk factors and management of TCR.[1,4,19–21] However, most of the earlier studies had smaller sample size as compared with our present study and their risk factors were often not collected specifically for the study, so that our study sheds for the first time, light on the problematic of a slight anesthesia as a risk factor for the TCR. With help of triangulation, we have also excluded confounders. In addition, our study would also serve as first systemic review on this topic and does open the door for further prospective studies related to TCR.

Unanswered Questions and Future Research

The TCR is already a well-known phenomenon during neurosurgeries and skull base procedures. But there are still many open questions about the treatment, the consequences and the risk factors of the TCR.

The trend of slight anesthesia being a risk factor for an increased intraoperative TCR manifestation is shown for the first time in this work. But this fact is still not sufficiently proved. There are needed a substantial higher number of publications about observed TCRs to clear this question in future expanded systematic reviews.

Currently, there is a strong deficit of studies including a large number of patients with reported details before, during, and after the TCR. It is important that future studies about the TCR publish detailed data about their patients (such as ASA, preoperative drugs, and depth of narcosis) for research of treatment and risk factors for the TCR on the one hand and of other questions about the TCR on the other hand. Only that way we can create new knowledge in niche research.[71] In our study, we often missed the information about the estimated depth of anesthesia (CSI) because of lack of knowledge about the used drugs or the detailed dose of the drugs in 27 out of 46 included publications (67 out of 140 patients). We hope therefore that the present study is also the beginning for further systematic literature reviews about the TCR in near future.

CONCLUSION

The present study is the first systematic literature review about the TCR. Because of the strict inclusion criteria, there is – despite different biases – a strong evidence of slight anesthesia to increased TCR/asystolia occurrence. In addition, the course of the TCR seems to be more pronounced under slight anesthesia. We have, additionally, introduced a new standard method to calculate the depth of anesthesia that should be used in every further TCR study and that makes it easier to compare different TCR studies each with the other.

Our current example points out the outstanding importance of case reports and case–control studies to improve medical knowledge not only in past centuries but also nowadays. But the consecutive growing complexity of the current knowledge needs further scientific methods such as meta-analysis to gain new and especially better evidence. We hope therefore that this systematic literature review may inspire others to publish and especially to deeply analyze their special cases that deal with not yet published clinical features of TCR; this is one of the most important ways that medicine can advance.

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Author's contribution: CM conducted the systematic review and written the manuscript. TC, NS, and MR gave substantial inputs for the review and during the writing process. PE and BS intensively supervised the work and substantially helped in the writing process. All authors read and approved the final manuscript.

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