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The trigeminocardiac reflex: the course of the emerged definition over the last 21 years

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The trigeminocardiac reflex (TCR), a unique brainstem reflex, was clinically described in skull base surgeries in the 90s [1] and since then, there has been a growing interest to explore this phenomenon further. Unfortunately, the precise definition of the TCR remains somewhat fuzzy impeding the TCR research. Currently, it is based on a relatively diffusion definition of the TCR: decrease in mean heart rate and/or mean arterial blood pressure by more than 20%. To reduce confounding factor-related biases, the clause of cause–effect relationship was introduced [1,2]. On the other hand, due to lack of randomized controlled studies on this topic, there still exists a substantial gap in level I or II evidence. Whether or not observational studies would be useful in such scenario needs to be explored in detail.

There are multiple pros and cons of this relatively strict initial definition of a more than 20% decrease of mean heart rate and mean arterial pressure after triggering of any of the sensory branches of the trigeminal nerve. This definition was used in most of the publications across all over the world as inclusion criteria [3,4], so this approach has provided some uniformity and standardization. However, it should be noted that such clinical observational studies usually have imminent methodological flaws including selection, randomization and confounding biases, introducing uncertainty of the old adage “*post hoc non propter hoc*”; not at least because of a lack of sufficient controls in the study protocol. In addition, the majority of observational studies are based on single centers, therefore lack global representation and reproducibility. It is also important to stress that these retrospective studies constitute a large body of TCR literature and possess all flaws of retrospective nature. Importantly, in some observational studies, few measures were taken to ensure that all subjects in the TCR and non-TCR groups receive the same intervention, either surgically or anaesthetically. Implementation of the standardizing measures to ensure minimum variability between the groups provides the advantage of higher internal validity and therefore more and often sufficient generalizability of the findings of the target and accessible population.

The inclusion of ‘confounders’ such as comorbidity or medications increases the variance and makes determination of β -error difficult. In the early TCR description [1], a detailed and defined ‘cause–effect relationship’ was mentioned and was later refined by Meuwly *et al.* [2]. In this context, the cause and effect modeling should be considered as a consecutive transient process [5] that can be utilized in TCR studies.

Within such conceptual frame of the scientific method (see Table 1), Schaller *et al.* [1] have initially defined several (transient) processes through which causation and effect could be established. That is why research design is such an important issue and why it is intimately linked to the idea of internal validity [5]. To establish empirical causation, the experiment must fulfill certain criteria (see Table 2). In an observational context, a mere observation of a correlation is not nearly adequate to establish causality [5], as the process through which such effects come about cannot be explained. In nearly all TCR cases, establishment of the causal process relies on repetition of experiments and probabilistic reasoning [1,2,5]. The scientific approach of “no causation without manipulation,” which was

Table 1. Advantages and disadvantages of strict inclusion criteria.

Advantages [1,3,4,8]	
Higher internal validity for clinical effects or adverse effects/tolerability	
Increased generalizability of the primary outcome	
Optimizing recruitment and follow-up of patients	
Disadvantages [1,3,4,9]	
Limit external validity	
Outcome measures may not reflect advantages/limitation of stimulation being studies	
Adapted from [4].	

Table 2. Prerequisites for establishing cause–effect relationships.

Plausibility	Activation of the TCR must be explained by stimulation of the trigeminal nerve The TCR must occur immediately following the stimulation
Reversibility	Removal of the stimulus abolished the TCR and cardiopulmonary measurements return to normal
Reproducibility	Re-applying the same stimulus results in a recurrence of the TCR Lighter stimulus of the same type does not activate the TCR
Prevention	Trigeminal nerve block eliminates the TCR Application of anticholinergic drugs blocks the reflex
TCR: Trigemino-cardiac reflex. Adapted from [2].	

put forth by Holland [6] more than three decades ago, has been a starting point of causal analysis and is also included in the initial definition by the ‘repetition/reproducibility’ clause. Also, Pearl proposed another dogma, “causation precedes manipulation” [7] reminding us that manipulation is merely a tool that is used by scientists to identify causal mechanisms and requires exclusion of plausible alternative explanations. Another way, also used in the initial publication, is to incorporate the use of a control group (“the non-TCR group”). These facts show that a clear initial concept of an observation with dichotomous end points, such as response (TCR) versus nonresponse (non-TCR), to an intervention (triggering of any of the sensory branches of the trigeminal nerve) overcome the flaws of observational nonrandomized research to show causation.

However, performance biases are especially seen in the systematic reviews or meta-analyses where the different anesthetic techniques may have another altering impact on the occurrence of TCR episodes. This is especially a problem in the case of the TCR [1,10], which has been described around the world for over more than two decades now. Here, the stringent inclusion criteria in a model-based selection (as used previously) is an established method [11]. Such a model-based approach of optimal inclusion criteria overcomes the probability of a type II error [12] by avoiding heterogeneity and therefore increases the reliability of the results. As such, the initial TCR strict inclusion criteria are a good example that early stage data can be used to create a suitable classification for discriminating responders (TCR) from nonresponders (non-TCR) [1,12]. Such adaptive approaches carry a risk of introducing bias into a trial. The magnitude of the statistical bias is practically negligible in many of TCR cases, and there are methods to counteract it. The best way to minimize operational bias is by rigorous planning and transparency.

However, this initial methodology [1] in the TCR research of a certain adaptive design is probably also the reason why this initial *ad-hoc* definition has lasted for more than 20 years. It is probably one of, if not the, first adaptive designs in observational study ever published, so that the initial TCR work of 1999 [1] is the cornerstone work, not only from the clinical point of view but also from the methodological point of view. It has helped that with a relatively small sample size, the initial report of the TCR [1] could be established with a good methodological quality, so that objectivity and replicability could be achieved.

In summary, over the last 21 years, there have been significant developments in the area of the TCR research. However, the definition of the TCR still remains largely unchanged and is being utilized worldwide. Few subconcepts and modifications in this definition were highlighted and it should be integrated into the previous well-defined definition of the TCR. This still remains the challenge. Therefore, our key message is that a meticulous adaptive methodological design should also be considered along with the robust clinical methodological approach in the TCR research. It is not the aim to just describe the methods, but rather to show how and why they are applied. This will open a platform for standardized research in TCR domain.

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