



# A-train clusters and the intermedius nerve in vestibular schwannoma patients



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## ARTICLE INFO

### Article history:

Accepted 13 February 2019

Available online 15 March 2019

### Keywords:

A-train

Vestibular schwannoma

Intraoperative monitoring

Intermedius nerve

Electromyography

## HIGHLIGHTS

- A-trains indicate facial nerve damage during intraoperative monitoring in vestibular schwannoma surgery.
- A separate intermedius nerve increases A-trains, partially occurring in cluster-like patterns.
- Intermedius nerve A-train clusters potentially confound intraoperative monitoring.

## ABSTRACT

**Objective:** EMG “A-train” activity correlates with postoperative facial palsy after vestibular schwannoma (VS) surgery. An intermedius nerve separate from the facial nerve increases A-trains without significant impact on function. We investigate occurrence of A-train “clusters”, A-trains over a majority of channels within a short time frame.

**Methods:** Data from 217 patients with first surgery for VS were evaluated retrospectively. Continuous EMG recorded with 9 channels was evaluated for A-train patterns. “Clusters” of A-trains were identified, i.e. A-trains within 3 seconds over a majority of channels. Relation to a separate intermedius, tumor size and facial palsy was evaluated.

**Results:** Correlations between A-trains and postoperative facial palsy were higher in patients without separate intermedius ( $r = 0.562$  versus  $r = 0.194$ ). Clusters were identified in 107 patients (49.3%), separate intermedius in 109 (50.2%), with significant association of both ( $p < 0.001$ , Chi-Square test). Excluding clusters slightly increased correlation of A-trains to facial nerve function.

**Conclusions:** A-train clusters have limited relevance for predicting postoperative paresis. However, they should be regarded as warning signs, suggesting the presence of a separate intermedius nerve.

**Significance:** A-train “clusters” are a sign of hyperactivity of the facial nerve due to a separate intermedius nerve and may confound intraoperative monitoring during VS surgery.

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## 1. Introduction

During surgery for vestibular schwannoma (VS) in the cerebello-pontine angle (CPA), damage to the facial nerve may lead to postoperative facial palsy. Severe facial palsy may require additional medical treatment, while moderate degrees may already impact quality of life (Samii and Matthies, 1997; Anderson et al., 2005). Different techniques for intraoperative monitoring (IOM) of facial nerve function are applied to minimize such complications, e.g. direct electric stimulation, motor evoked potentials and

continuous EMG (Delgado et al., 1979; Harner et al., 1987; Sterkers et al., 1994; Samii et al., 2006; Acioly et al., 2013).

In previous studies, we have demonstrated that a specific pathological pattern in the free-running EMG is related to acute damage to the nerve (Romstöck et al., 2000; Rampp et al., 2007; Prell et al., 2010). These “A-train” patterns (Fig. 1) appear as rhythmic trains of muscle action potentials of few or single motor units and reach frequencies between approx. 60–210 Hz. Amplitudes amount to 100–200  $\mu$ V and rarely reach 500  $\mu$ V, however significantly depend on placement and number of recording electrodes (Rampp et al., 2012). The total quantity (“train time”) is correlated to the degree of postoperative facial palsy (Prell et al., 2007, 2010, 2014, 2015; Rampp et al., 2011, 2013).

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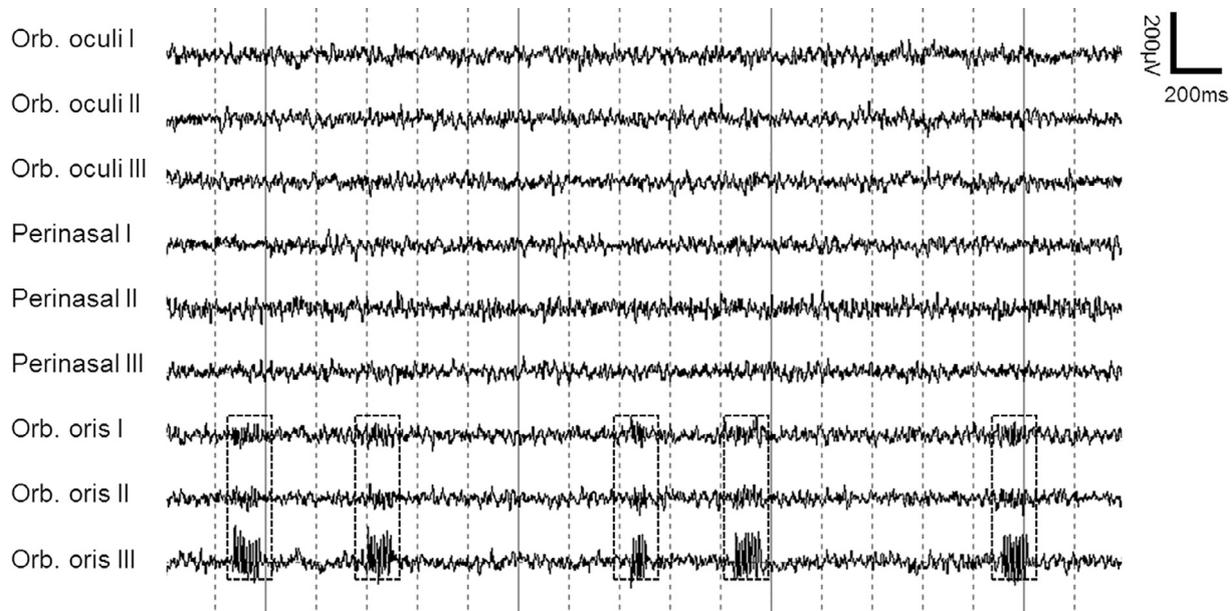


Fig. 1. Example of non-cluster A-trains. Similar to Fig. 2 (different patient), A-trains are visible in neighboring channels (Orb. oris).

In some patients with VS, the facial nerve displays a distinct splitting along its course through the CPA (Strauss et al., 2006). We later argued, that the smaller portion may represent the intermedium nerve, while still carrying motor fibers especially to the perinasal muscles, as well as to the orbicular oris muscle (Alfieri et al., 2014). Such a separate intermedium nerve has consequences not only for the surgical strategy (Strauss et al., 2006; Alfieri et al., 2012), requiring identification of both portions, but also impacts IOM using free-running EMG. In a series of 87 cases, we demonstrated that patients with a separate intermedium nerve are significantly more likely to present considerable “false-positive” train time without a corresponding functional correlate (Prell et al., 2015). Furthermore, damage to the intermedium nerve is rarely associated with more than subtle deficits (Mowry et al., 2012; Rodgers et al., 2014).

Differentiation of A-trains generated by the facial vs. the intermedium nerve would potentially limit the impact of false positive detection. While direct electric stimulation shows some differences between the two nerves (Ashram et al., 2005; Alfieri et al., 2014), distinguishing features in free-running EMG have not yet been identified.

In the current study, we present evidence that the distribution of intermedium A-trains is frequently more diffuse and extended in comparison to A-trains generated by the facial nerve. Evaluation of this distribution pattern may contribute to identify and minimize false-positive A-trains.

## 2. Methods

### 2.1. Patients

A series of 217 consecutive patients undergoing surgery for vestibular schwannoma (VS) surgery between 2006 and 2017 were evaluated retrospectively. Inclusion criteria were first surgery for VS, adult age, availability of continuous intraoperative EMG information regarding tumor size, as well as pre- and postoperative facial nerve function according to the House-Brackmann grading system (HB) (House and Brackmann, 1985). Exclusion criteria were previous radiosurgery and diagnosis of neurofibromatosis.

All patients gave their written informed consent. The study was approved by the local institutional review board (ethics committee

of the medical faculty, Martin-Luther-University Halle (Saale), Germany).

### 2.2. Identification of a separate intermedium nerve

Presence or absence of a separate intermedium nerve was determined either intraoperatively by the surgeon or evaluated based on intraoperative videos with simultaneous EMG recordings. Criteria for identification were identical to our previous study (Prell et al., 2015): a clear bundle of neural tissue with a course separate from the main portion of the facial nerve within the CPA and merging with it at the porus acusticus internus and/or a clear response in facial muscles after electrical stimulation in an area unrelated to the known facial nerve course with emphasis of the lower face. Characteristics of the EMG were not used for identification of a separate intermedium nerve.

### 2.3. Recordings

Continuous EMG was recorded using a Grass-Telefactor 15LT biosignal amplifier (West Warwick, Rhode Island) and proprietary recording system described earlier (Prell et al., 2010). Filtering was limited to a 5 Hz high-pass filter. Data were digitized using a sampling rate of 6485 Hz using a National Instruments PCI-6229 A/D-card (Austin, Texas). A total of 9 bipolar channels were recorded from electrodes placed in the ocular oris, peri nasal and orbicular oris muscles (3 channels per muscle group).

Recording started before skin incision and continued without interruption until the end of the surgical procedure. Real-time analysis of the EMG data for A-train activity (Prell et al., 2010) was performed as part of our in-house routine.

### 2.4. Evaluation of facial nerve function

Pre- and postoperative facial nerve function was evaluated by a single experienced evaluator (author JP) based on standardized photographs and using the grading system according to House and Brackmann (1985). Author JP was also a member of the surgical team, however results regarding A-train clusters were not available for the evaluation.

## 2.5. Analysis

In addition to the automated intraoperative procedure, all channels of the complete datasets were inspected visually for A-train activity and manually marked by a technical assistant with extensive experience in IOM and specifically free-running EMG.

Segments of data were marked that showed extensive A-train activity over a majority of the nine channels (“A-train cluster”) within a time frame of up to 3 seconds and only short pauses (Fig. 2). This simultaneous A-train activity could persist for longer durations. We did not differentiate cluster vs. non-cluster A-trains regarding amplitude, frequency and morphology of the individual trains. The pattern definition and hypothesis, that such patterns may constitute a differentiating feature was based on observations during manipulations in the vicinity of a separate intermedius nerve, as well as on results of a previous study, which found similar “false-positive” patterns in patients with previous VS surgery or radiotherapy (Rampp et al., 2013). Total train time was related to postoperative outcome including and excluding segments with A-train clusters using Spearman correlations.

Statistical analysis then evaluated the association of A-train cluster occurrence in a recording with presence of a separate intermedius nerve using chi-square tests. Influence of tumor size was evaluated using logistic regression analysis. All calculations were performed using SPSS Statistics software (Version 25.0., IBM Corp, Armonk, NY, USA).

## 3. Results

### 3.1. Patients

Of the 217 patients, 122 were female (56%). Average age at surgery was 50 years, ranging from 22 to 80 years. Median tumor size was Koos grade 3. Median preoperative HB grade was 1 (range 1–3, 1st quartile 1, 3rd quartile 2). Median HB degree after surgery was 2 (range 1–5, 1st quartile 2, 3rd quartile 3). After 6 months, facial nerve outcome improved to a median of HB 1 (range 1–5, 1st quartile 1, 3rd quartile 2).

A separate intermedius nerve was identified in 109 of the 217 patients (50.2%) and was associated with tumor size ( $p < 0.001$ , Chi-square test, Fig. 3). The latter was especially obvious in patients with small (Koos 1) tumors, in whom a majority of patients did not display a separate intermedius nerve (18 vs. 2 patients), and in cases with Koos 3 tumors, where this was reversed (27 vs. 48). The overall outcome of patients with and

without a separate intermedius nerve did not differ significantly ( $p > 0.1$  after surgery and after 6 months, Mann-Whitney-U-test).

### 3.2. A-trains

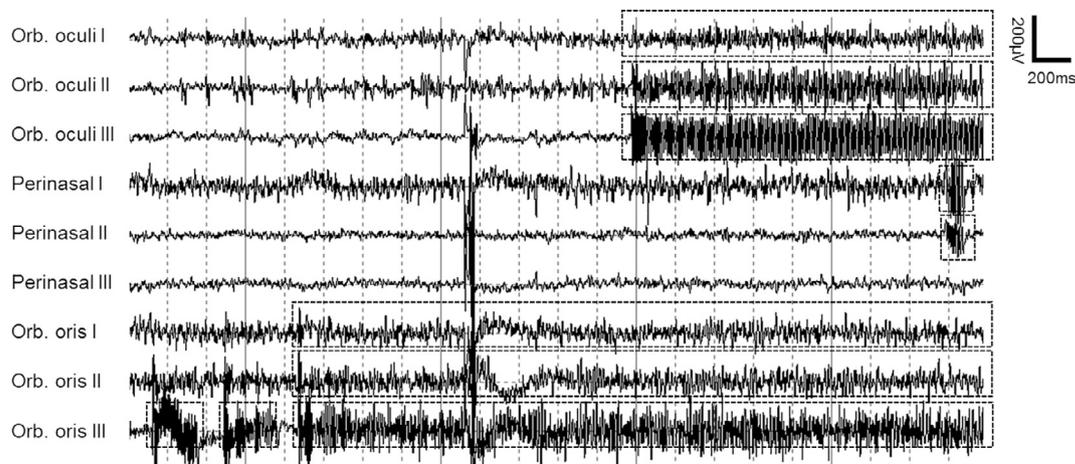
Total train time significantly correlated with postoperative degree of facial palsy (Spearman correlation,  $r = 0.388$ ,  $p < 0.001$ ), as well as 6 months after surgery ( $r = 0.289$ ,  $p < 0.001$ ). In the subgroup of patients without a separate intermedius nerve, correlations were higher ( $r = 0.562$ ,  $p < 0.001$  after surgery,  $r = 0.513$ ,  $p < 0.001$  after 6 months) in comparison to patients with a separate nerve ( $r = 0.194$ ,  $p = 0.044$  after surgery). In the latter group, correlations to facial nerve function after 6 months were not significant ( $p > 0.1$ ). Total train time also showed a significant correlation to tumor size ( $r = 0.502$ ,  $p < 0.001$ , Spearman correlation). Frequency, duration and morphology of A-trains did not show any obvious differences between patients with and without separate intermedius nerve.

A-train clusters were identified in 107 patients (49.3%). Occurrence of this pattern was significantly associated with a separate intermedius nerve ( $p = 0.0022$ , Chi-square test), however also occurred in patients without. Patients with clusters had worse outcome than patients without ( $p < 0.001$  after surgery,  $p = 0.004$  after 6 months, Mann-Whitney-U-test), as well as larger tumors ( $p < 0.001$ ), which was also reflected by higher train time values ( $p = 0.001$ , t-test). The percentage of patients with clusters increased steadily with tumor size (Fig. 4), deviating from detection of a separate intermedius nerve. A logistical regression analysis of detection of A-train clusters with the factors train time and tumor size revealed distinct influences of both. I.e. while larger tumors are associated with larger train times, the occurrence of A-train clusters is an effect exceeding this interaction. Adjusting for tumor size in a second logistical regression analysis confirmed an independent influence of presence of a separate intermedius nerve ( $p = 0.026$ ).

Excluding segments with A-train clusters increased the correlation of remaining train time to facial nerve function ( $r = 0.424$ ,  $p < 0.001$  versus  $r = 0.388$ ,  $p < 0.001$  after surgery,  $r = 0.319$ ,  $p < 0.001$  versus  $r = 0.289$ ,  $p < 0.001$  after 6 months), however the differences were small.

## 4. Discussion

Our data demonstrates that patients with a separate intermedius nerve show more diffuse, “clustered” A-train activity dur-



**Fig. 2.** Example of an A-train cluster: Numerous A-train patterns within approx. 2.5 s. The bipolar channels record from neighboring contacts within a region. A-trains within a region may thus be visible simultaneously in several channels. All three regions and 8 of 9 channels show activity.

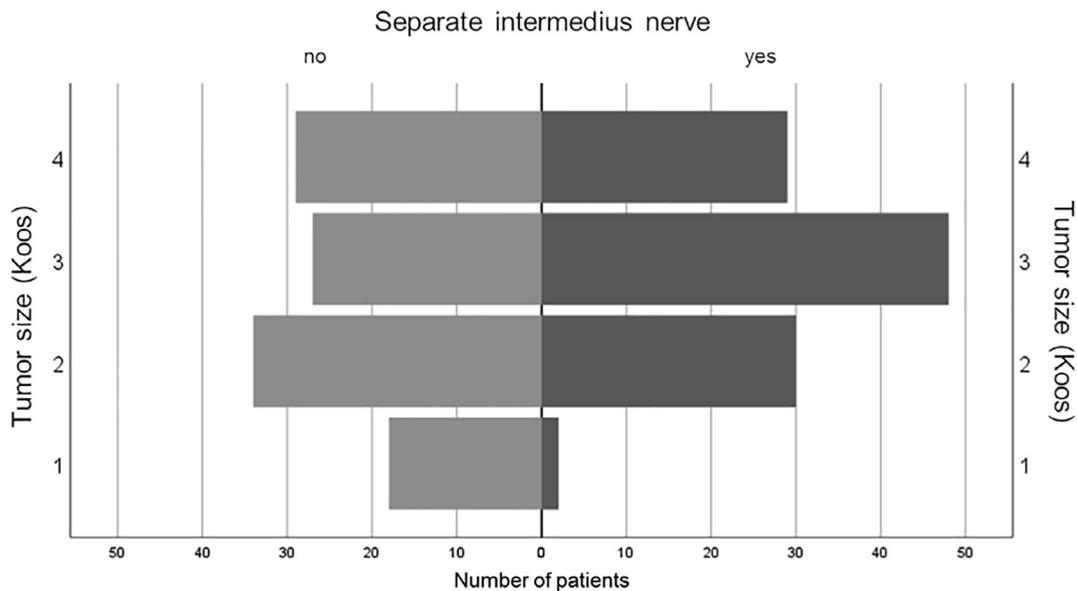


Fig. 3. Observation of a separate intermedius nerve and tumor size.

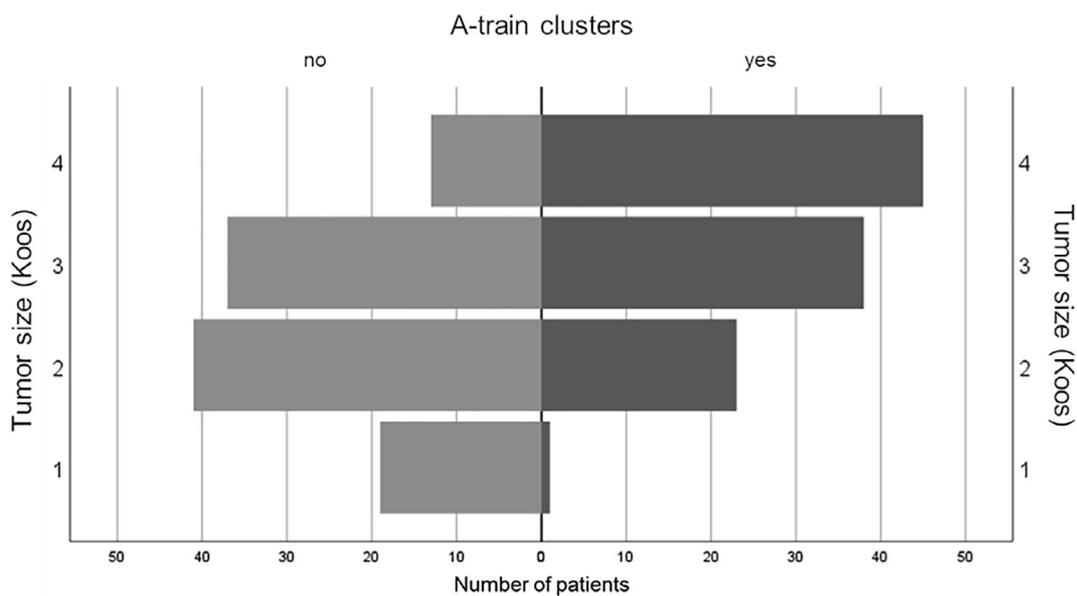


Fig. 4. Presence of A-train clusters and tumor size.

ing VS surgery. In contrast, facial nerve function is not affected in a corresponding manner, suggesting that clustered A-trains may at least partially include false-positive activity. Vice versa, occurrence is indirect evidence hinting at a separate intermedius nerve, with the corresponding implications for monitoring and the surgical strategy.

The likeliness for A-train clusters to occur increases with larger tumor size. Due to the increased surgical difficulty, larger tumors are also associated with higher train time values. Logistical regression however demonstrated that A-train clusters cannot be explained completely as an epiphenomenon of increasing train time.

Larger tumors were also more likely to present with a separate intermedius nerve. However, this peaked in the group with Koos 3 tumors and decreased again in larger VS. Such large tumors may however further mechanically displace and rarefy a separate intermedius, rendering identification difficult or impossible.

This could then result in additional vulnerability with more intermedius A-train and A-train clusters.

As the presence of A-train clusters is associated with the identification of an intermedius nerve by the surgeon, one has to wonder if this positive detection of a structure not considered to be of paramount importance for facial nerve outcome might indirectly explain the elicitation of A-train clusters. A potentially brisker manipulation as compared to what one would do to the proper facial nerve might activate/damage a large portion of the motor fibers carried by the intermedius nerve (Alferi et al., 2012, 2014) all at the same time, which could very well be represented by the observed A-train clusters.

Clusters, however, were also observed in patients without a separate intermedius nerve. The diffuse occurrence of A-train patterns in a short time segment may thus not be exclusively caused by a vulnerable intermedius nerve. Simultaneous damage to several nerve fibers in the proper facial nerve during dissection

could in principle lead to the same electrophysiological appearance. This may also explain, why the difference in correlation of train time to facial nerve function improves only slightly when A-train clusters are removed. The removed train time may contain relevant “non-intermedius” A-trains which would be suggestive of damage to the facial nerve. The improvement resulting from this strategy thus has unfortunately rather limited practical value. In addition, an extended montage with a comparably high number of channels (Prass et al., 1987; Rampp et al., 2012) is necessary to recognize A-train clusters, which further limits practicability. The findings may however be a first step towards classification of intermedius nerve A-trains, in the absence of almost any other distinguishing feature.

Ashram et al. (2005) reports low amplitude, long latency responses to electric stimulation of the intermedius nerve, which allows the differentiation from the facial nerve. This however requires direct access to the nerves. Direct value for the classification of A-trains or any other pattern in the free-running EMG has not been demonstrated. It remains therefore unclear, whether stimulation could be used to identify putative intermedius nerve A-trains and subsequently exclude those from facial nerve monitoring.

In a previous paper (Alfieri et al., 2014), we also reported differences in the topography of stimulation responses. These were emphasized in perinasal and perioral regions. This response pattern was also used in the present study for identification of a separate intermedius nerve. Identification by stimulation only may represent a potential source of bias and lacks the robustness of visual identification. It may therefore be possible that few of the detected intermedius nerves may in fact have been mistaken to follow a course separate from the main facial nerve trunk. However, such misinterpretations would decrease the contrast between patients with and without separate intermedius and would not argue against our results.

The diffuse distribution of A-trains clusters thus seems to contradict the findings of Alfieri et al. (2014). However, A-trains likely reflect the activity of single motor units. Thus, only few aberrant fibers to the perioral region may be enough for the generation of A-train clusters. In contrast, electric stimulation likely activates the complete stimulated bundle, which certainly may show a preference for caudal facial muscles.

The phenomenon of A-train clusters is reminiscent of the pattern observed in patients undergoing IOM and surgery for recurrent VS after previous microsurgery or radiotherapy (Rampp et al., 2013). In this study, we argued that especially prior radiotherapy may have induced microstructural changes in the facial nerve, leading to hyperexcitability, however without any obvious clinical correlate. This is supported by A-train-like myokymic activity after radiation of cranial and spinal nerves (Nagano et al., 2008). Patients with previous surgery also displayed hyperexcitability, however to a lower extent. Different mechanisms like rarefaction, scarring and changes of vascularization may be responsible for diffuse A-train activity in this population. Since a separate intermedius nerve would also be exposed to mechanical strain by the growing tumor mass, similar processes may lead to the observed A-train clusters, which also seem to have no clear clinical correlate.

## 5. Conclusions

In conclusion, A-train clusters have limited relevance for predicting postoperative paresis. However, they should still be regarded as warning signs, suggesting the presence of an intermedius nerve with a course separate from the facial nerve.

## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) (PR1275/1-2).

## Declaration of interest

None of the authors have potential conflicts of interest to be disclosed.

## References

- Acioly MA, Liebsch M, de Aguiar PHP, Tatagiba M. Facial nerve monitoring during cerebellopontine angle and skull base tumor surgery: a systematic review from description to current success on function prediction. *World Neurosurg* 2013;80:e271–300.
- Alfieri A, Fleischhammer J, Peschke E, Strauss C. The nervus intermedius as a variable landmark and critical structure in cerebellopontine angle surgery: an anatomical study and classification. *Acta Neurochir (Wien)* 2012;154:1263–8.
- Alfieri A, Rampp S, Strauss C, Fleischhammer J, Rächinger J, Scheller C, et al. The relationship between nervus intermedius anatomy, ultrastructure, electrophysiology, and clinical function. Usefulness in cerebellopontine microsurgery. *Acta Neurochir (Wien)* 2014;156:403–8.
- Anderson DE, Leonetti J, Wind JJ, Cribari D, Fahey K. Resection of large vestibular schwannomas: facial nerve preservation in the context of surgical approach and patient-assessed outcome. *J Neurosurg* 2005;102:643–9.
- Ashram YA, Jackler RK, Pitts LH, Yingling CD. Intraoperative electrophysiologic identification of the nervus intermedius. *Otol Neurotol* 2005;26:274–9.
- Delgado TE, Bucheit WA, Rosenholtz HR, Chriatian S. Intraoperative monitoring of the facialis muscle evoked responses obtained by intracranial stimulation of the facialis nerve: a more accurate technique for facialis nerve dissection. *Neurosurgery* 1979;4:418–21.
- Harner SG, Daube JR, Ebersold MJ, Beatty CW. Improved preservation of facial nerve function with use of electrical monitoring during removal of acoustic neuromas. *Mayo Clin Proc* 1987;62:92–102.
- House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Neck Surg* 1985;93:146–7.
- Mowry S, Hansen M, Gantz B. Surgical management of internal auditory canal and cerebellopontine angle facial nerve schwannoma. *Otol Neurotol* 2012;33:1071.
- Nagano O, Higuchi Y, Serizawa T, Ono J, Matsuda S, Yamakami I, et al. Transient expansion of vestibular schwannoma following stereotactic radiosurgery. *J Neurosurg* 2008;109:811–6.
- Prass RL, Kinney SE, Hardy Jr RW, Hahn JF, Luders H. Acoustic (loudspeaker) facial EMG monitoring: II. Use of evoked EMG activity during acoustic neuroma resection. *Otolaryngol Head Neck Surg* 1987;97:541–51.
- Prell J, Rächinger J, Scheller C, Alfieri A, Strauss C, Rampp S. A real-time monitoring system for the facial nerve. *Neurosurgery* 2010;66:1064–73. discussion 1073.
- Prell J, Rampp S, Romstöck J, Fahlbusch R, Strauss C. Train time as a quantitative electromyographic parameter for facial nerve function in patients undergoing surgery for vestibular schwannoma. *J Neurosurg* 2007;106:826–32.
- Prell J, Strauss C, Rächinger J, Alfieri A, Scheller C, Herfurth K, et al. Facial nerve palsy after vestibular schwannoma surgery: dynamic risk-stratification based on continuous EMG-monitoring. *Clin Neurophysiol* 2014;125.
- Prell J, Strauss C, Rächinger J, Scheller C, Alfieri A, Herfurth K, et al. The intermedius nerve as a confounding variable for monitoring of the free-running electromyogram. *Clin Neurophysiol* 2015;126:1833–9.
- Rampp S, Prell J, Rächinger JC, Scheller C, Strauss C. Does electrode placement influence quality of intraoperative monitoring in vestibular schwannoma surgery? *Cent Eur Neurosurg* 2011;72:22–7.
- Rampp S, Prell J, Thielemann H, Posch S, Strauss C, Romstöck J. Baseline correction of intraoperative electromyography using discrete wavelet transform. *J Clin Monit Comput* 2007;21:219–26.
- Rampp S, Rächinger J, Scheller C, Alfieri A, Strauss C, Prell J. How many electromyographic channels do we need for facial nerve monitoring? *J Clin Neurophysiol* 2012;29.
- Rampp S, Strauss C, Scheller C, Rächinger J, Prell J. A-trains for intraoperative monitoring in patients with recurrent vestibular schwannoma. *Acta Neurochir (Wien)* 2013;155:2273–9. discussion 2279.
- Rodgers B, Chamoun R, Newell K, Lin J. Nervus intermedius meningioma. *J Laryngol Otol* 2014;128:543–6.
- Romstöck J, Strauss C, Fahlbusch R. Continuous electromyography monitoring of motor cranial nerves during cerebellopontine angle surgery. *J Neurosurg* 2000;93:586–93.
- Samii M, Gerganov V, Samii A. Improved preservation of hearing and facial nerve function in vestibular schwannoma surgery via the retrosigmoid approach in a series of 200 patients. *J Neurosurg* 2006;105:527–35.
- Samii M, Matthies C. Management of 1000 vestibular schwannomas (acoustic neuromas): the facial nerve–preservation and restitution of function. *Neurosurgery* 1997;40:684–5.
- Sterkers JM, Morrison GA, Sterkers O, El-Dine MM. Preservation of facial, cochlear, and other nerve functions in acoustic neuroma treatment. *Otolaryngol Head Neck Surg* 1994;110:146–55.
- Strauss C, Prell J, Rampp S, Romstöck J. Split facial nerve course in vestibular schwannomas. *J Neurosurg* 2006;105:698–705.