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Editorial II

Muscle relaxation and depth of anaesthesia: where is the missing link?

In the last few years, several monitors have been developed to assess the depth of anaesthesia and to discriminate between its pharmacodynamic components. Most of those monitors have been initially designed to assess the hypnotic component of anaesthesia. Experience has progressively revealed that several factors other than external artifacts can alter the interpretation of what is said to be the depth of anaesthesia, that is, the value of the indices.[1] Among those factors, the pharmacodynamic interaction between anaesthetic agents plays a key role,[2] and neuromuscular blocking agents (NMBAs) can, theoretically, be involved in that interaction. The calculation of depth of anaesthesia indices is frequently based on EEG recordings. The frequency band associated with EMG activity is close to that of the EEG. As NMBAs modulate EMG activity, they may artificially modify the calculated index[3] or suppress valuable information from the signal. Given these theoretical considerations, the variability of the algorithms involved in the calculation of indices, and the limited evidence-based information, actually predicting how a given index may be affected by neuromuscular block during anaesthesia is not easy. Specific studies are needed to address this issue.

Influence of muscle relaxation on depth of anaesthesia

In 1946, Gray and Halton[4] first suggested that NMBA may affect the depth of the hypnotic or the antinociceptive components of anaesthesia. As NMBAs cross the blood–brain barrier to a very small extent, a hypothetical effect on depth of anaesthesia can only be explained by indirect mechanisms [Fig. 1: (1) and (2)]: the reduction in the amount of proprioceptive inputs to the brain emerging from peripheral muscles and a direct central effect of NMBA metabolites.

The first mechanism refers to the de-afferention theory. It has been demonstrated that sensory deprivation causes a decrease in EEG power and a shift towards slower frequencies.[5] A reduction in the amount of proprioceptive inputs to the reticulo-thalamic activating system would reduce the level of arousal[6] and explain why NMBA administered in dogs during an isoflurane-induced burst suppression pattern significantly increased the periods of isoelectricity.[7] However, muscle relaxation does not produce complete sensory deprivation. Should such an effect exist in humans, it would be poorly detectable, and

probably overwhelmed by other sensory inputs or any arousing effect of central origin such as anxiety or attention. Indeed, the i.v. administration of NMBA to volunteers as a sole medication provokes a decrease in BIS without any change in the median frequency or total power of the EEG,[8] and this decrease is less marked in anxious volunteers. In addition, in volunteers receiving an intermediate level of propofol-alone anaesthesia with low EMG activity, muscle relaxation does not seem to modify the hypnotic level, as assessed by BIS.[9 10]

Regarding the second mechanism, NMBAs are devoid of anti-nociceptive properties. However, atracurium and cisatracurium are metabolized into laudanosine, which can cross the blood–brain barrier and be detected, at clinically relevant concentrations, in the cerebrospinal fluid,[11] mainly after prolonged infusions. This metabolite has μ-related anti-nociceptive properties in the mouse[12] and is also able to activate central nicotinic receptor subtypes, which elicit analgesic activity.[13] Hence, laudanausine could theoretically deepen the anti-nociceptive level and affect cortical activity, but no direct clinical proof of this is available in humans.

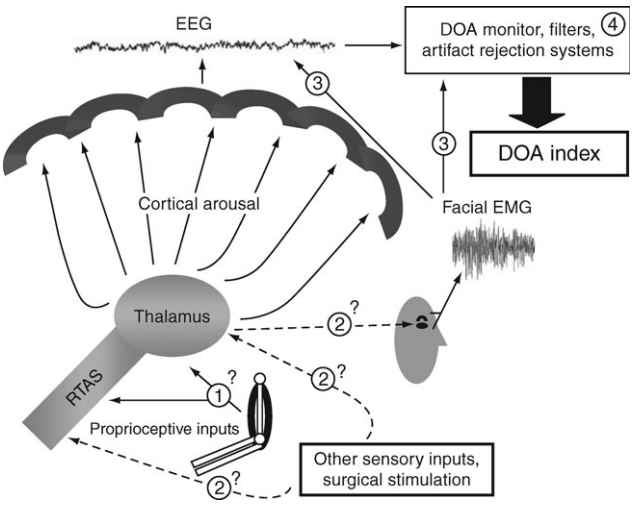

Fig 1 Schematic representation of possible mechanisms through which muscle relaxation may influence depth of anaesthesia (DOA), or what is measured as depth of anaesthesia (DOA index). (1): muscle relaxation may reduce muscle tone and proprioceptive afferences to the brain (speculative). (2): atracurium or metabolites such as laudanosine may have anti-nociceptive properties, limit nociceptive inputs, and facial EMG responses to nociceptive stimulation (speculative). (3): muscle relaxation reduces facial EMG activity. 4: DOA monitor algorithm, filters, and artifact rejection systems will determine to what extent the calculation of the depth of anaesthesia index value will be affected by EMG activity and muscle relaxation.

Effect of muscle relaxation on the calculation of depth of anaesthesia indices

Depth of anaesthesia indices are calculated from filtered and digitalized EEG frames through complex algorithms. Several variables are extracted from either a time or a frequency domain analysis of the tracing. These variables are then combined into a normalized dimensionless index varying between 0 and 100. The frequency composition of the EEG and the EMG partially overlaps in the 30–50 Hz range.[9] Independently of efficient filtering, EMG contamination in unconscious individuals may mimic the EEG of awake subjects and influence the value of the variables entering the calculation algorithm of a given index [Fig. 1: (3)]. The variables differ from one index to another. Therefore, the influence of EMG will not be the same for all indices [Fig. 1: (4)]. That influence will also depend on the type of filters and artifact rejection systems implemented into the monitor and the frequency band reflecting the EMG activity[14] (Table 1). Finally, as the EMG frequency band is part of the calculation of some indices, the suppression of EMG activity by muscle relaxation will remove valuable information from the signal [Fig. 1: (4)].

Frequency bands of interest and artifact rejection algorithms

Bispectral index

Since its first commercial availability, the bispectral index (BIS) algorithm has undergone a number of revisions mainly designed to improve handling of suppression-like EEG tracings and rejection of artifacts such as electrocautery, eye movements, and EMG activity. In contrast to the previous ones, the new version of artifact rejection (BIS XP and later versions) recognizes an artifact from its asymmetry with a mirror image recorded from a supplementary electrode. Although this system is efficient at removing artifacts of electrocautery or eye movement, it does not rule out possible contamination by facial EMG.[15] Indeed, an important variable entering the BIS calculation is the so-called BetaRatio. It is calculated on a frequency range that overlaps EMG frequencies in the 30–47 Hz interval. EMG frequencies can therefore mimic the 30–47 Hz component of the BetaRatio and be interpreted by the monitor as a typical activity of the awake state or light anaesthesia. This would be seen in cases with high muscle tone, such as opioid-induced muscle rigidity.[16] Simply filtering out the high-frequency components of the EEG (that is above 30 Hz) to avoid EMG contamination would remove important information about the level of hypnosis, as high-frequency gamma-band oscillations in the EEG (40–60 Hz) are important markers of the conscious state.[17] Consequently, it is important to be aware of the EMG activity when observing spurious changes in BIS, in order to correctly interpret those modifications.

Spectral entropy of the electroencephalogram

The spectral entropy of the EEG as obtained with the M-Entropy Module quantifies the degree of irregularity and chaos of the EEG signal. It provides two values: the state entropy and the response entropy. The state entropy

Table 1 Summary of the characteristics of available depth of anaesthesia monitors with regards to EMG activity and influence of muscle relaxation on the value of the index. Frequency band: main EEG frequency band concerned by the index calculation. EMG: frequency band whose activity is interpreted by the monitor as EMG activity (not always available from the manufacturer). Parameter: EEG-derived subparameter whose value is most probably influenced by muscle relaxation or EMG activity. Muscle relaxation: main effect of muscle relaxation on the value of the index. Studies: main studies having specifically investigated this point. N/A, not applicable; ?, no available data

Monitor	Company	Index	Frequency band (Hz)	EMG (Hz)	Parameter	Muscle relaxation	Studies
A2000™/BIS, XP™/ BIS, VISTA™	Aspect Medical Systems	Bispectral index (BIS™)	1–47	70–110	BetaRatio	↓↓ if high EMG activity present	Liu and colleagues[19] Dahaba and colleagues[10] Messner and colleagues[8] Renna and colleagues[16] Greif and colleagues[9]
M-Entropy™	Datex-Ohmeda	State entropy (SE)	0.8–32	32–47	N/A	Not substantial	Liu and colleagues[19] Vereecke and colleagues[14]
	Datex-Ohmeda	Response entropy (RE)	0.8–47	32–47	Entropy linked to facial EMG activity (32–47 Hz)	↓↓ RE–SE response to stimulation	Hans and colleagues[27]
AEP Monitor™	Danmeter A/S	A-Line ARX Index (AAI™)	N/A	65–85	N/A	?	?
AEP Monitor/2™	Danmeter A/S	Composite AEP/EEG AAI™	10–47	65–85	Power in the 30–47 Hz band?	↓↓	Vereecke and colleagues[14]
Narcotrend™	MonitorTechnik	Narcotrend™	0.5–45	?	?	?	?
SEDLine™/PSA 4000™	Hospira	Patient state index (PSI™)	0.5–50	?	?	?	?
SNAP II™	Everest biomedical instruments	SNAP II™	0–420	?	?	?	?
CSM Monitor™	Danmeter A/S	Cerebral state index (CSI™)	6–42.5	?	?	?	?

is computed over the EEG dominant part of the frequency spectrum, that is, 0.8–32 Hz. It is thought to reflect the cortical state, and hence the level of hypnosis, and ranges between 0 and 91. The response entropy is computed over a larger frequency range (0.8–47 Hz) which includes the spectrum covering both EEG and EMG. It is always higher or equal to the state entropy and ranges between 0 and 100.[18] The state entropy has been reported to be less influenced by muscle relaxation than BIS.[14 19] The absence of a substantial effect of muscle relaxation on the state entropy is not surprising when considering the respective frequency bands. On the other hand, muscle relaxation has a much greater influence on the response entropy and on the gradient between the response entropy and the state entropy (discussed later).

The A-Line autoregressive index

The A-Line autoregressive index (AAI) is derived from middle latency auditory evoked potentials and combines information extracted from the EEG power spectrum and from the burst suppression activity with the previously used auditory information to generate a composite index varying between 0 and 100.[20] Little is known about the effect of muscle relaxation on the auditory-alone version of the AAI, but rocuronium has been demonstrated to decrease the newer AAI 1.6 value under steady-state anaesthetic conditions.[14] This is not surprising as the EEG frequency range in the algorithm is 10–47 Hz, hence partly covering EMG activity. It would be interesting to compare the effect of muscle relaxation on both indices (old and new version) recorded simultaneously and determine the relative impact of EMG activity decrease on that effect.

Other available monitors

Several other depth of anaesthesia monitors are available (Table 1). Very few studies have assessed the effect of muscle relaxation on the value of their index, although most of them can, theoretically, be influenced by EMG activity. The Narcotrend monitor combines selected time domain and frequency domain EEG parameters.[21] Its frequency band of interest is 0.5–45 Hz. Advanced artifact rejection algorithms are implemented to detect artifacts caused by muscle activity and reject typically contaminated epochs.[22] However, no specific study has addressed the effect of muscle relaxation on the Narcotrend index. This is also true for the patient state index, which relies on EEG power, frequency, and phase information from antero-posterior relationships, and coherence between brain regions of both sides.[23] This monitor is equipped with advanced artifact rejection algorithms, and its frequency band of interest is 0.5–50 Hz. The SNAP index is calculated from the analysis of high (80–420 Hz) and low (0–20 Hz) frequency components of the EEG.[24] It is probably influenced by high-frequency EMG activity, but this point still needs to be clarified. Finally, the cerebral state index extracts information from the 6–42.5 Hz

frequency band and from burst suppression activity to combine them into a 0–100 dimensionless index.[25] The influence of muscle relaxation on that index is not known.

Influence of electromyographic activity on the agreement between indices

Two different depth of anaesthesia indices agree when they indicate the same anaesthetic state in the same patient at a given time. As mentioned earlier, muscle relaxation may influence each of the available depth of anaesthesia indices in different ways. Hence, muscle relaxation may also affect their agreement. For example, it has been demonstrated that the agreement between BIS and state entropy, although globally poor, is good only in awake patients and in paralysed patients.[26] The change in agreement between BIS and state entropy in different clinical situations (awake, paralysed…) may be related to several factors including EMG activity and its differential influence on BIS and state entropy calculation. This is also probably true for other depth of anaesthesia monitors, but this has still to be investigated.

Suppression of information through suppression of electromyographic activity

In addition to the influence of muscle relaxation or EMG activity on depth of anaesthesia indices, which may generate spurious values, inhibition of EMG activity by muscle relaxation may also suppress valuable information from the recorded signal. For example, the gradient between the response entropy and the state entropy, which is supposed to reflect the nociceptive–anti-nociceptive balance, is highly dependent on the degree of muscle relaxation. The response of this gradient to a standardized nociceptive stimulation is greatly attenuated or even suppressed by muscle relaxation.[27] It can therefore be inferred either that muscle relaxation may suppress information of interest or that the monitor is not appropriate for such information in a paralysed patient. To our knowledge, the response entropy is the only commercially available depth of anaesthesia index in which facial EMG activity is included in the calculation algorithm.

Reversal of muscle relaxation and depth of anaesthesia

Neostigmine is used widely to antagonize non-depolarizing muscle relaxants and it does not cross the blood–brain barrier. However, under steady-state anaesthetic conditions and stable level of hypnosis, the administration of neostigmine appears to increase the value of BIS and AAI.[28] The mechanisms through which neostigmine may affect the depth of hypnosis or the value of depth of anaesthesia indices are not known. Three hypotheses may be proposed: an effect on brain acetylcholine levels, an effect on EMG activity, and an effect on proprioceptive inputs. Although neostigmine crosses the blood–brain barrier poorly, it may enter the brain, increase synaptic acetylcholine availability and provoke an arousing effect such as physostigmine,[29] but this mechanism is not likely. Through its effect on muscle tone, neostigmine could increase EEG contamination by EMG and artificially increase the value of the index. This hypothesis is not likely either. Indeed, the preliminary administration of NMBA did not change BIS or AAI, despite a decrease in EMG activity.[28] Furthermore, neostigmine increased not only BIS, but also AAI, which is thought to be much less influenced by EMG activity. In a recent study,[30] the administration of the novel cyclodextrin-derived antagonist of steroid NMBA, sugammadex, which does not modify acetylcholine turnover and does not cross the blood–brain barrier, was associated with an increase in BIS and signs of awakening such as grimacing, sucking, movement, and coughing. Therefore, something other than an increase in EMG activity must account for such an effect. The last hypothesis refers to the influence of proprioceptive inputs. As mentioned earlier, the influence of proprioceptive inputs on the level of arousal is probably weak at the onset of neuromuscular block, but could be of importance at the time of reversal, under light anaesthetic conditions. This question remains unanswered.

Conclusions

What we measure as depth of anaesthesia can be influenced by muscle relaxation, possibly through direct effects of NMBA on the depth of the hypnotic or anti-nociceptive components of anaesthesia themselves, and more probably through their effect on the EMG activity of facial muscles whose frequency domain partly overlaps the EEG frequency domain. The consequences are two-fold: the possibility of spurious depth of anaesthesia indices, which are not related to the depth of anaesthesia, and loss of important information from the analysed signal. The effects of NMBA on depth of anaesthesia indices values will depend on the type of monitor used, its calculation algorithm, filters, and artifact rejection systems. There is still a need for studies to clearly characterize the effect of muscle relaxation on available depth of anaesthesia indices.

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