EJA

Eur J Anaesthesiol 2021; **38**:1 – 11

ORIGINAL ARTICLE

Age, minimum alveolar concentration and choice of depth of sedation monitor: examining the paradox of age when using the Narcotrend monitor

A secondary analysis of an observational study

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BACKGROUND With an ageing global population, it is important to individualise titration of anaesthetics according to age and by measuring their effect on the brain. A recent study reported that during general surgery, the given concentration of volatile anaesthetics, expressed as a fraction of the minimum alveolar concentration (MAC fraction), decreases by around only 3% per age-decade, which is less than the 6% expected from age-adjusted MAC. Paradoxically, despite the excessive dosing, Bispectral index (BIS) values also increased.

OBJECTIVE We planned to investigate the paradox of age when using the Narcotrend depth of anaesthesia monitor.

DESIGN Secondary analyses of a prospective observational study.

SETTING Tertiary hospital in Switzerland, recordings took place during 2016 and 2017.

PATIENTS One thousand and seventy-two patients undergoing cardiac surgery entered the study, and 909 with noise-free recordings and isoflurane anaesthesia were included in this analysis.

INTERVENTION We calculated mean end-tidal MAC fraction and mean index value of the Narcotrend depth of sedation monitor used in the study during the prebypass period. Statistical associations were modelled using linear regression, local weighted regression (LOESS) and a generalised additive model (GAM).

MAIN OUTCOME MEASURES Primary endpoints in this study were the change in end-tidal MAC fraction and mean Narcotrend index values, both measured per age-decade.

RESULTS We observed a linear decrease in end-tidal MAC fraction of 3.2% per age-decade [95% confidence interval (CI) −3.97% to −2.38%, $P < 0.001$], consistent with previous findings. In contrast to the BIS, mean Narcotrend index values decreased with age at 3.0 index points per age-decade (95% CI, −3.55 points to −2.36 points, $P < 0.001$), a direction of change commensurate with the increasing age-adjusted MAC fraction with patient age. These relationships were consistent regardless of whether age-adjusted MAC was displayed on the anaesthetic machine.

CONCLUSIONS We caution that the ‘paradox of age’ may in part depend on the choice of depth of sedation monitor.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02976584.

Published online xx month 2021

Introduction

Increasing age is associated with numerous cardiovascular, hepatic, renal and respiratory changes,[1] as well as with changes in the central nervous system, such as axon depletion and decreased brain volume[2] and cortical thickness.[3] Unsurprisingly, anaesthetic requirements also decline with increasing age. When measured by the minimum alveolar concentration (MAC), defined as the anaesthetic dose at which half the population will remain immobile to a 2 cm incision, volatile anaesthetic dosing requirements decrease by about 6% per additional

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DOI:10.1097/EJA.0000000000001576

decade of age.[4] This robust finding has been repeatedly verified.[5–7] Precision dosing of anaesthesia in older patients is especially important considering the demographic shift to an older society and the controversial possibility that excessive anaesthetic dose in older patients could increase the likelihood of postoperative delirium and long-term cognitive dysfunction.[8–10]

The dose-dependent effect of anaesthetics on the brain in adults and children can best be evaluated by a raw and quantitative electroencephalogram (EEG), as has been frequently reported over the past century.[11–15] Although a range of intriguing findings have recently been published on the effect of age on EEG features during anaesthesia,[16–20] in the clinical situation anaesthesia providers still very often depend on a depth of sedation or depth of anaesthesia index as a key variable to guide anaesthetic titration. EEG-based depth of sedation monitors use various EEG parameters to calculate and display an index number typically between 0 (coma) and 100 (awake), purporting to represent depth of hypnosis during anaesthesia. Several monitors are available on the market, such as the Bispectral Index (BIS, Covidien, Dublin, Ireland) or the Narcotrend Monitor (Monitor-Technik, Bad Bramstedt, Germany) and most keep the details of the index calculation proprietary, although there have been repeated calls for this to change.[21–23]

A significant contribution to the literature on age and anaesthetic dosing when using a depth of sedation monitor index has been recently published by Ni *et al.*[24] In this noteworthy study, completed at a single North American institution, the investigators observed that when the concentration of volatile agents was expressed as proportion of their MAC (MAC fraction), there was a decrease in MAC fraction given of only around 3% per age-decade, in contrast to the 6% expected from published reports, and as confirmed by their own recent meta-analysis.[7] This raised the question of whether older patients are, therefore, receiving excessive doses, of around 3% per age-decade.[25] Paradoxically, in the Ni study, the BIS index values increased with age, which if correct implies an underdosing of older patients. The disparity between the MAC fraction and the depth of sedation monitor values raises a host of important questions.[25,26] First, is the observed potential overdosing (according to the MAC fraction) a local phenomenon restricted to the single study site, or perhaps attributable to North American clinical practice? And second, is the potential underdosing (according to the BIS) a generalised phenomenon, or restricted to the particular brand of depth of sedation monitor used?

Our dataset of a previous study allowed us to closely replicate the work of Ni and colleagues but in a European hospital and with a different brand of depth of sedation monitor (the Narcotrend Monitor). In addition, in our dataset we were also able to retrospectively determine whether patient age had been correctly entered into the machine settings (Primus, Draeger, Lübeck, Germany), which if entered displays an age-adjusted MAC (aaMAC) fraction for each patient. Our goal was to investigate if the delivered end-tidal MAC fraction decreases by less than the expected 6% per age decade, if the Narcotrend index values also show a paradoxical increase with age, and if the MAC fraction given with increasing age differs depending on whether the age-adjusted MAC is displayed.

Patients and methods

We used prospectively collected data from an observational trial (ClinicalTrials.gov Identifier: NCT02976584). The STROBE checklist for observational studies was used to guide the methods used in this analysis and to structure the manuscript.[27]

Ethical approval for this study (KEK#210/15) was provided by the Ethics Committee of the Canton of Bern (Kantonale Ethikkommission für die Forschung, Murtenstrasse 31, Bern, Switzerland) on the 4 November 2015.

Electroencephalographic analysis

One thousand and seventy-two patients were included who had undergone general anaesthesia for cardiac surgery between July 2016 and November 2017 at the Bern University Hospital (Inselspital) in Bern, Switzerland. Electrodes of an EEG-based depth of sedation monitor (Narcotrend, MonitorTechnik, Bad Bramstedt, Germany) were attached to the patients' foreheads according to the manufacturer's instructions (electrodes positioned at FP1-TP9, Fpz as common reference). Electrode impedance levels were kept below 5 kΩ for the duration of the recording.

Narcotrend index values were extracted from Philips IntelliVue MP90 anaesthesia monitors (Philips Medical Systems, Eindhoven, Netherlands) and the end-tidal volatile anaesthetic concentration extracted from the anaesthetic machine (Primus; Draeger, Luebeck, Germany) using the Rugloop II software (Demed Medical, Temse, Belgium). End-tidal isoflurane concentrations were recorded every 3 s and interpolated to every second in Matlab (R2016a, The MathWorks, Inc., Natick, Massachusetts, USA). Although Ni and colleagues used the entire surgical period, this was not feasible in our dataset because of inexact end-tidal values during cardiopulmonary bypass (CPB), and cases of hypothermia. Therefore, we restricted our analysis to the period prior to CPB, which showed a stable EEG. Any recordings for which core body temperature was less than 34 °C for more than 5 min before CPB were excluded from the analysis. Following Ni and colleagues, we only analysed patients older than 30 years. In contrast to Ni and colleagues, we chose to allow pre-CPB periods shorter than 1 h (but longer than 10 min), as the anaesthesia dosing and EEG were generally stable during these periods.

Patients who had received sevoflurane or propofol as primary anaesthetic agent were excluded from the analysis because of the small group sizes. The MAC of isoflurane was considered as 1.17%, and the age-adjusted MAC fraction was as detailed in Ni *et al.* [24] based on Mapleson.[4] The Narcotrend index value was sometimes missing because of noise; the pre-CPB period had to have at least 50% of the analysis time-period with index values present to be included in the analysis. Patients who had had their age entered into the Draeger machine by the anaesthesia provider (which then displayed age-adjusted MAC) were compared with patients who had not, where the machine displayed MAC_{40} (MAC for a 40 year old).

Statistical analysis

No power analysis was completed for this study, as it is a retrospective analysis of data from an observational study. The statistical analysis used the R Project for Statistical Computing package (https://www.r-project.org),[28] and effect sizes were reported with 95% confidence intervals (95% CI). The overall statistical approach followed that of Ni *et al.* [24] so that our results obtained with the Narcotrend monitor were as comparable as possible to their results using the BIS. Following Ni and colleagues, for the Narcotrend index and end-tidal MAC fraction, we first took the averages of 1 min blocks, then the median of these over 5 min, finally taking the average of the subsequent median values over the entire pre-CPB period.

The relationship between age, mean MAC fraction and Narcotrend index was graphically portrayed and ordinary least squares linear regression was used to model the relationship between age and MAC fraction, age and aaMAC fraction and age and Narcotrend index. The relationships were also modelled using a generalised additive model (GAM) and local weighted regression (LOESS) to help visualise departure from linearity.

We also portrayed the relationship between the Narcotrend index and aaMAC fraction stratified into three age groups (31 to 49, 50 to 75 and ≥76 years) using segmented regression with two breakpoints.[29] A multivariable linear regression was performed on age-adjusted MAC fraction with the variables total dose of rocuronium given during the operation, BMI, gender and total sufentanil dose during the operation.

Results

Of the 1072 patients in our database, 36 were excluded from analysis because of missing data over the pre-CPB period, and 48 received propofol or sevoflurane anaesthesia. A further 15 were excluded as they were younger than 31 years, 6 were repeat recordings, 12 had temperatures less than 34 °C in the pre-CPB period and 38 had less than 50% Narcotrend index values available prior to CPB. A further eight patients who had pre-CPB periods shorter than 10 min were also excluded from analysis. The remaining 909 patients all received isoflurane as their primary anaesthetic agent. Patient age was entered correctly into the anaesthetic machine for 423 patients (47%) and was not entered for 486 (53%) (Fig. 1).

Descriptive data

In our study, the median [range] age was 67 [31 to 86] years. The group consisted of 701 men (77%). Median weight was 81 [40 to 144] kg, median height was 172 [147 to 196] cm and median BMI was 26.8 [16.4 to 46.1] kg m^{-2}. The median length of pre-CPB period was 72 [11 to 233] min. Only 90 patients (9.9%) had pre-CPB recordings of less than 30 min. The mean ± SD MAC over the pre-CPB period was 0.66 ± 0.14, and the mean age-adjusted MAC was 0.77 ± 0.16. The mean Narcotrend index value was 42 ± 10.

Main findings

The MAC fraction decreased significantly at 3.2% (95% CI, −4 to −2.4%, $P < 0.001$) per age-decade (adjusted $R^2 = 0.06$) (Fig. 2), matching results of Ni and colleagues. Table 1 shows the results of all linear regression models against age.

The age-adjusted MAC fraction increased significantly with age, at 1% (95% CI, 0.1 to 2%, $P = 0.028$, $R^2 = 0.04$) per age-decade using OLS regression (Fig. 3).

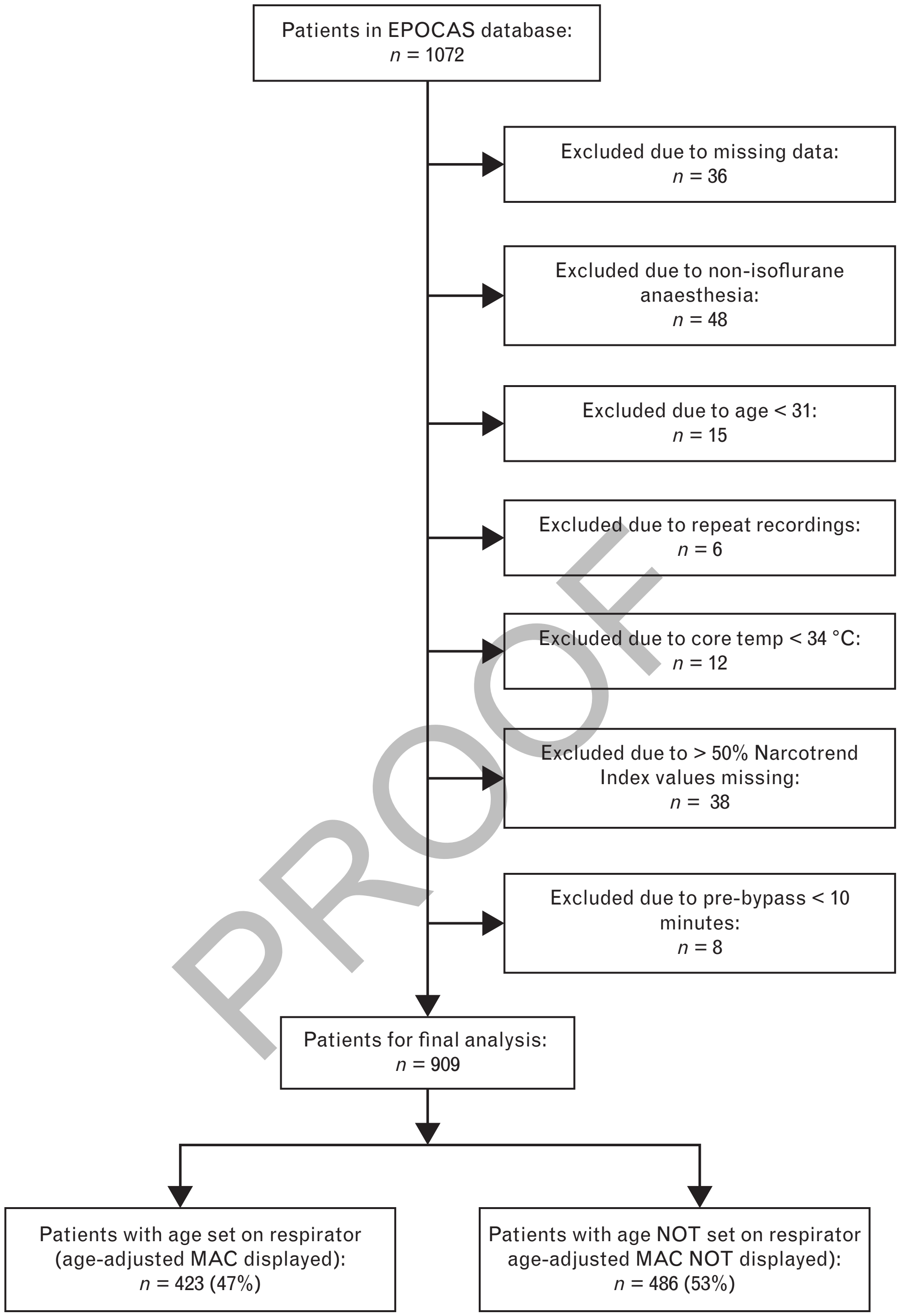
The Narcotrend Index decreased by 3 index points (95% CI, −3.6 points to −2.4 points, $P < 0.001$, $R^2 = 0.10$) per age-decade in the linear regression (Fig. 4). This is in contrast to the increasing BIS index values with age reported by Ni and colleagues.

The mean Narcotrend Index values seem visually stable in response to increasing aaMAC fraction for the two patient age groups younger than 75 years (Fig. 5). In contrast, in patients older than 75 years, there was a slight visual positive association between mean Narcotrend index value and aaMAC fraction administered, when mean aaMAC fractions administered were between 0.5 and 0.9. Mean differences in Narcotrend Index value between the three age groups, and Cohen's *d* values to illustrate effect size are shown in the Supplemental Digital Content Table 1, http://links.lww.com/EJA/A594.

The magnitude of the MAC fraction reduction with age and also the Narcotrend index reduction with age remained the same regardless of whether age was set on the machine and displayed as an age-adjusted MAC, or not (Fig. 6). Specifically, the MAC fraction given decreased by 3.2% (95% CI, −4.3 to −2.0%, $P < 0.001$) per age-decade when age was NOT set in the respirator, and by 3.1% (95% CI, −4.2% to −2.1%, $P < 0.001$) per age-decade when it was. Similarly, the Narcotrend Index value decreased by 2.6 index points per age-decade (95% CI, −3.4 to −1.8 points, $P < 0.001$) when age was NOT set in the machine, and by 3.4 index points per age-decade (95% CI, −4.3 to −2.5 points, $P < 0.001$) when it was.

There was no significant effect of rocuronium dose, BMI or sufentanil dose on the age-adjusted MAC fraction in

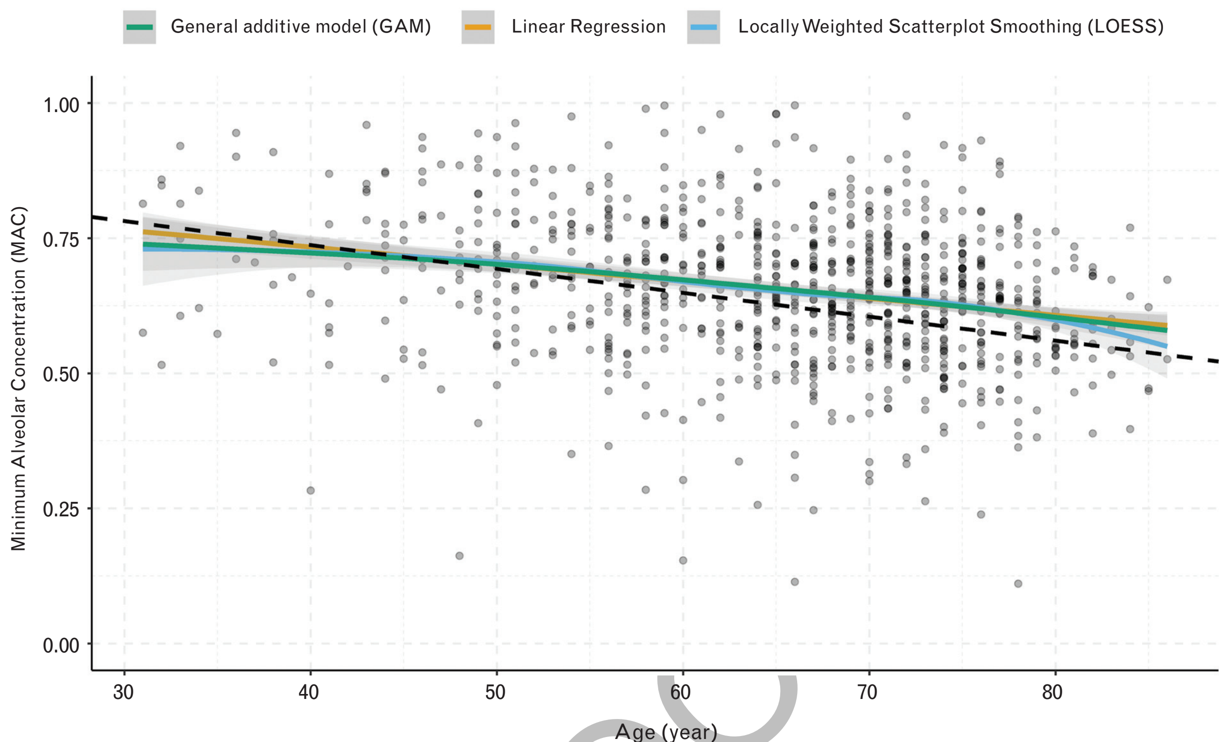
Fig. 1 Flow diagram showing reasons for patient exclusion from analysis.



the linear multivariable analysis (all P values >0.05, Table 2). A small gender effect was noted, where female patients were given slightly less age-adjusted MAC fraction than male patients.

In a supplementary analysis, we found that age had a significant effect on the MAC fraction, but that the addition of sufentanil alone, and the interaction term of age and sufentanil were not statistically significant (Supplementary

Fig. 2 The relationship between mean minimum alveolar concentration fraction given and age visualised by linear regression (orange line), a generalised additive model (green line) and LOESS (blue line).



Grey bands denote the 95% confidence intervals. Grey dots represent individual patients. As reference, the black dashed line refers to a 6% decadal decrease in MAC relative to a 40-year-old patient. MAC, minimum alveolar concentration.

Digital Content, Table 2, http://links.lww.com/EJA/A594), indicating that older patients were not receiving a lower MAC fraction because they had been given a higher opioid dose.

Discussion

Our retrospective analysis of patients undergoing cardiac surgery at a single Swiss tertiary hospital shows a linear decrease in the end tidal MAC fraction given of 3.2% per age-decade, consistent with the findings of Ni *et al.*[24] in the North American context, but less than the 6% decrease expected from the literature.[6,7] In contrast, index values of the depth of sedation monitor we used, the Narcotrend Index, did not increase with age as seen with the BIS, but rather decreased with age, a direction of change in line with the increasing *age-adjusted* MAC fraction with patient age. Interestingly, these relationships remained the same regardless of whether age-adjusted MAC was displayed on the anaesthetic machine.

Table 1 **Results of the linear regressions against age, showing beta coefficients, 95% confidence intervals for beta, *P* values, and adjusted R^2**

Linear regression	Beta coefficient (per age-decade)	95% confidence intervals	*P* value	Adjusted R^2
Age versus MAC	−3.2%	−4.0% to −2.4%	<0.001	0.06
Age versus aaMAC	1%	0.1% to 2.0%	0.028	0.04
Age versus Narcotrend Index	−3.0 points	−3.6 to −2.4 points	<0.001	0.10
Age versus MAC (age NOT set)	−3.2%	−4.3% to −2.0%	<0.001	0.05
Age versus MAC (age set)	−3.1%	−4.2% to −2.1%	<0.001	0.07
Age versus Narcotrend Index (age NOT set)	−2.6 points	−3.4 to −1.8 points	<0.001	0.07
Age versus Narcotrend Index (age set)	−3.4 points	−4.3 to −2.5 points	<0.001	0.12

aaMAC, age-adjusted minimum alveolar concentrationas a proportion of the age adjusted minimum alveolar concentration; MAC, minimum alveolar concentration as a proportion of the minimum alveolar concentration at age 40 years.

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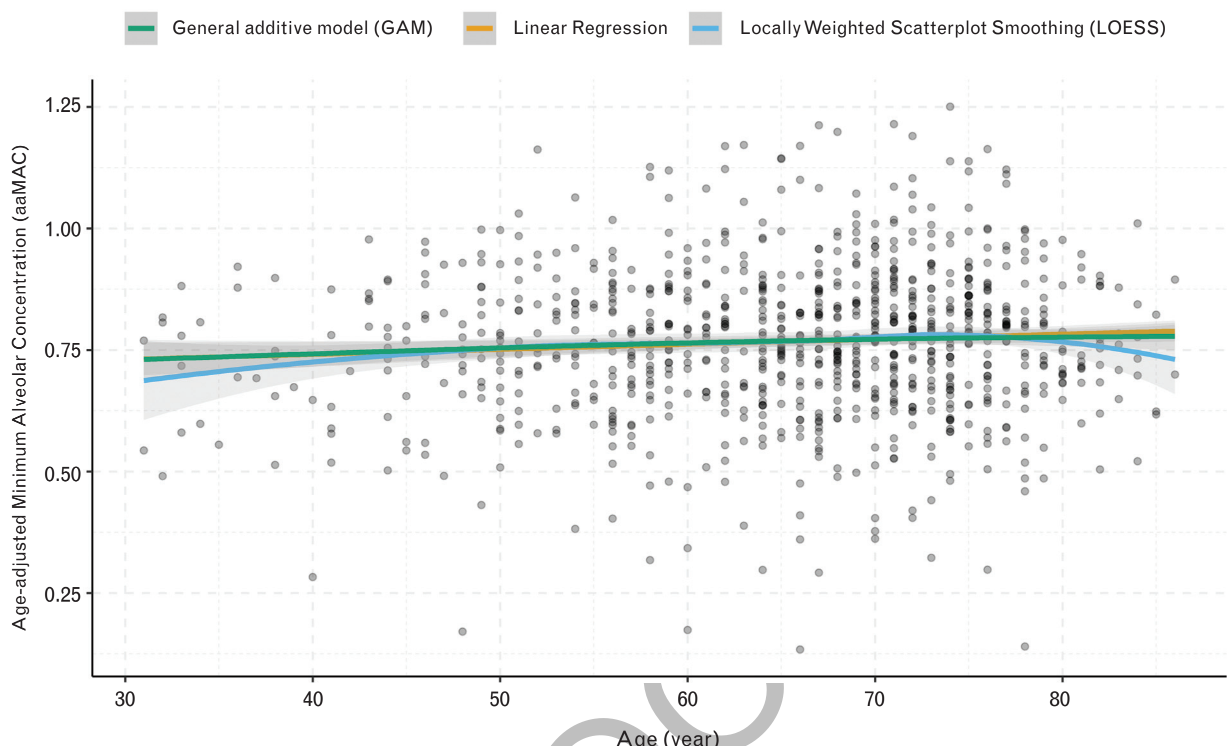
Fig. 3 The relationship between age-adjusted minimum alveolar concentration fraction and age visualised by linear regression (orange line), a generalised additive model (green line) and LOESS (blue line).

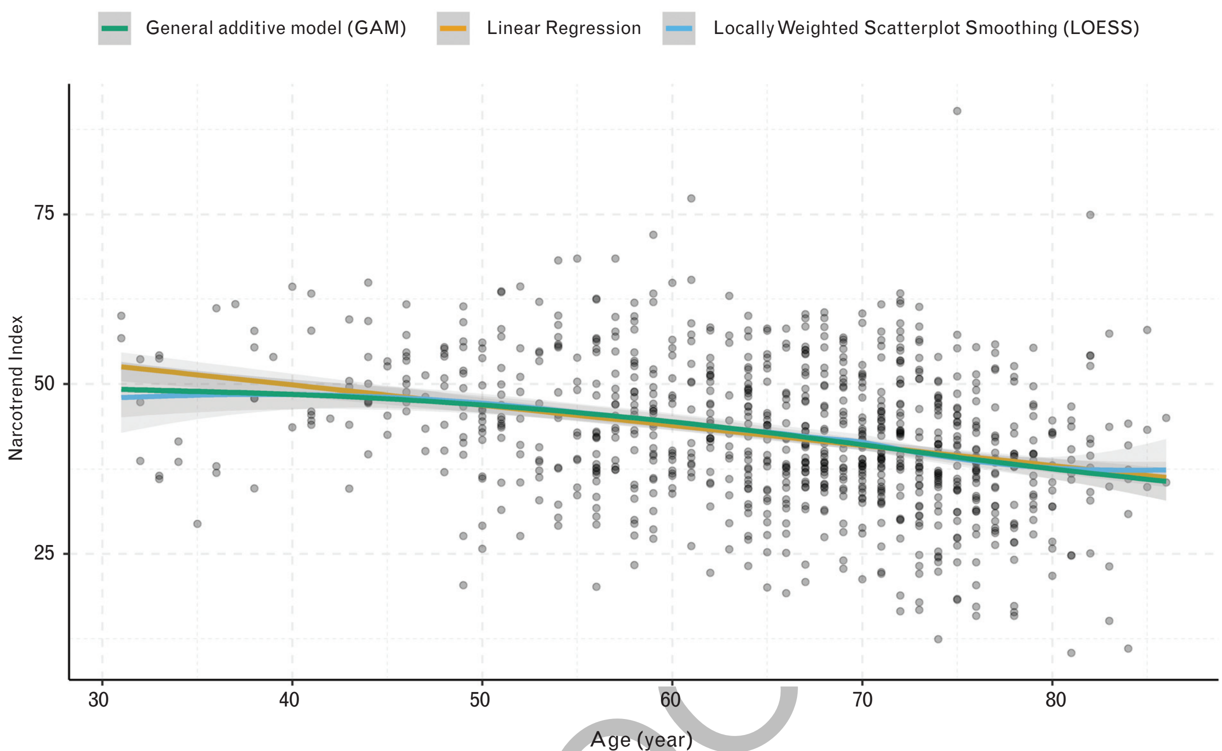


Grey bands denote the 95% confidence intervals and grey dots represent individual patients. aaMAC, age-adjusted minimum alveolar concentration.

The 'paradox of age' present when using the BIS is no longer evident in our data using the Narcotrend monitor, despite very similar MAC fraction reductions with age between the two groups. This observed difference provides support for the original suggestion [24] that the source of the age-paradox lies in the details of the BIS algorithm, not in the EEG itself, nor in the age adjustment of the MAC measure. Although it has been suggested that perhaps the BIS is more trustworthy (as a measure of cortex drug effect) than the anaesthetic dose required to achieve one MAC (as a measure of spinally mediated drug effect on immobility) with increasing age,[26] our findings speak against this. That the Narcotrend index decreases with age, a direction of change corresponding to the insufficient reduction of MAC fraction with age, whereas the BIS does not, shows that commercial indexes cannot be considered as unproblematic 'measures' of cortex drug effect. Depth of sedation monitors, sometimes also named perhaps less accurately 'depth of anaesthesia' monitors, [30] provide numerical estimates of patient sedative or hypnotic state derived from combinations of various EEG variables. It is well known that commercial indices are not drug invariant, can be oversensitive to muscle activity,[31] have differing responses to EEG patterns representing increasing dose,[32,33] and as our data now suggest, respond differently to increasing age.

There has been comparatively little research on the Narcotrend monitor, and the information on the EEG indices the algorithm uses is sparse.[34] The Narcotrend Monitor, developed in Germany and commercially available in Europe since 2000, initially used spectral features and autoregressive modelling to compare with visual classification of anaesthesia states according to a sleep-based staging system.[35] The algorithm has been updated over the years, and includes unspecified amplitude, spectral, autoregressive and entropic variables derived from the EEG to determine the index value.[36,37] The Narcotrend monitor does require users to enter age before generating an index value, but might only use age to adjust index values in children. Like all monitors, it has its own limitations, such as a high index absence rate,[38] but it does seem to outperform the BIS in adjusting for age. Despite previous suggestions that the BIS and Narcotrend monitors are broadly equivalent, there have

Fig. 4 The relationship between Narcotrend Index and age visualised by linear regression (orange line), a generalised additive model (green line) and LOESS (blue line).



Grey bands denote the 95% confidence intervals and grey dots represent individual patients.

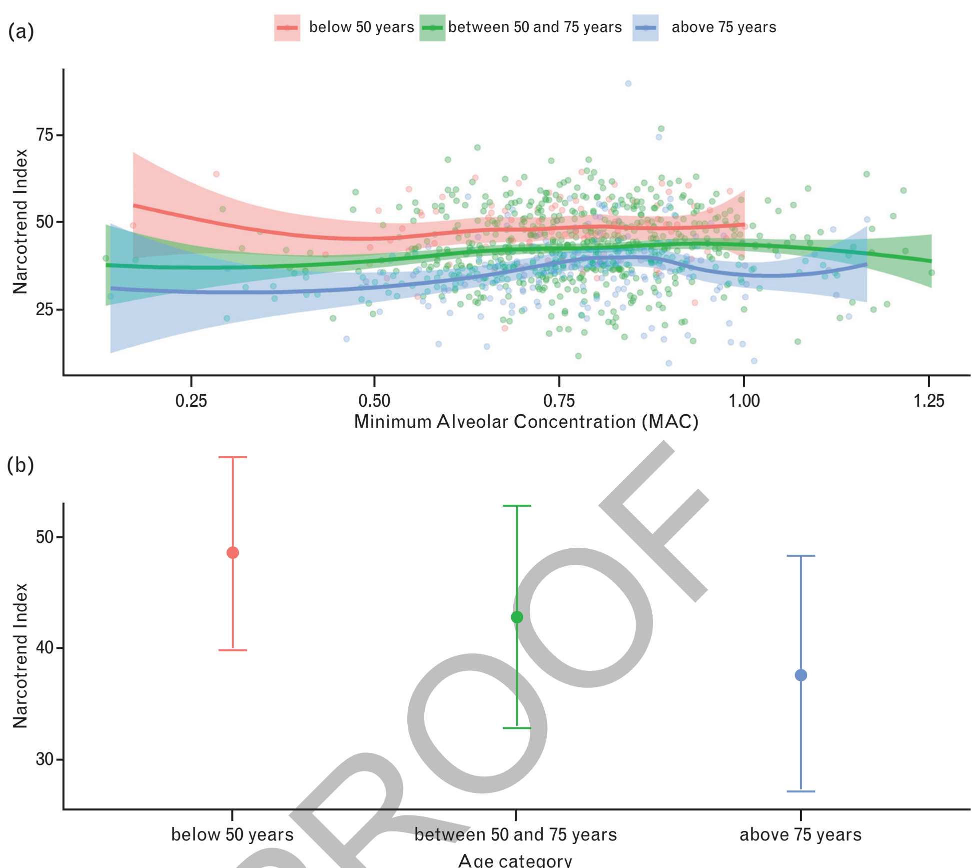
been contradictory reports.[38] Until companies publish their algorithms, scientists and clinicians alike are left in the dark as to which EEG signal changes lead to which index changes, and thus to the accuracy of these vital clinical indicators.[21,22] Ultimately, it may be perhaps most beneficial to look at the raw EEG or spectrogram to better guide anaesthetic titration.[12,13,16,39]

There are also good reasons to question the accuracy of the BIS with increasing age, based on known EEG changes with age, and primarily the increased relative power in high frequency ranges, as has been well noted before.[18,25,33,40] This increased power in the higher frequency ranges may be because of a decreasing broadband 1/*f* spectral effect, which is also reflected in entropic measures (increased entropy).[18] We agree with Kreuzer *et al.*[18] that future depth of sedation algorithms need to either account for age, or use EEG variables that are impervious to the effects of ageing.

Our data showed that when age-adjusted MAC was displayed, it had no effect on dosing modifications with age, confirming the suspicion that the relative 'overdosing' in the age-adjusted MAC fraction is not because of the simple engineering issue of whether the aaMAC is displayed or not.[25] In this context, it is also important to note that as the Narcotrend Index decreased with age, we can deduce that anaesthesia providers were not using the index as a guide to dosing with increasing age. If anaesthesia providers were adjusting dosing with age according to the index value, we would expect the counterfactual finding that the Narcotrend index would not decrease with age, and that the MAC would therefore, decrease at something closer to 6% per age-decade. This leads us to conclude that considerations other than the age-adjusted MAC and Narcotrend index took precedence in managing clinical dose.

Regarding effect sizes, the overall decrease in MAC fraction with age we observed (3.2%) is not only in agreement with that reported by Ni *et al.*[24] (3.01%) but also with a previous study[41] that noted an analogous effect in adults older than 65 years (3.8%) but less so in younger patients (1.8%). As has been noted by others, this seemingly small difference in MAC fraction reduction per age-decade of 3.2 versus 6.5% is not clinically irrelevant, as effects sum linearly over age-decades, and thus might lead to unnecessarily high dosing of elderly patients, with potential side

Fig. 5 (a) Narcotrend Index plotted against age-adjusted minimum alveolar concentration fraction using the LOESS method for local regression fitting when patients are stratified into age groups (below 50 years, between 50 and 74 years, and above 75 years). Individual dots refer to individual patients and shaded bands denote the 95% confidence interval. (b) Pairwise comparisons of the Narcotrend Index by stratified age categories, where the means (±1 standard deviation) are shown for each age category. Mean differences and Cohen's *d* values are shown in the Supplemental Digital Content, Table 1, http://links.lww.com/EJA/A594.



effects including intra-operative hypotension and possibly postoperative delirium or cognitive dysfunction.

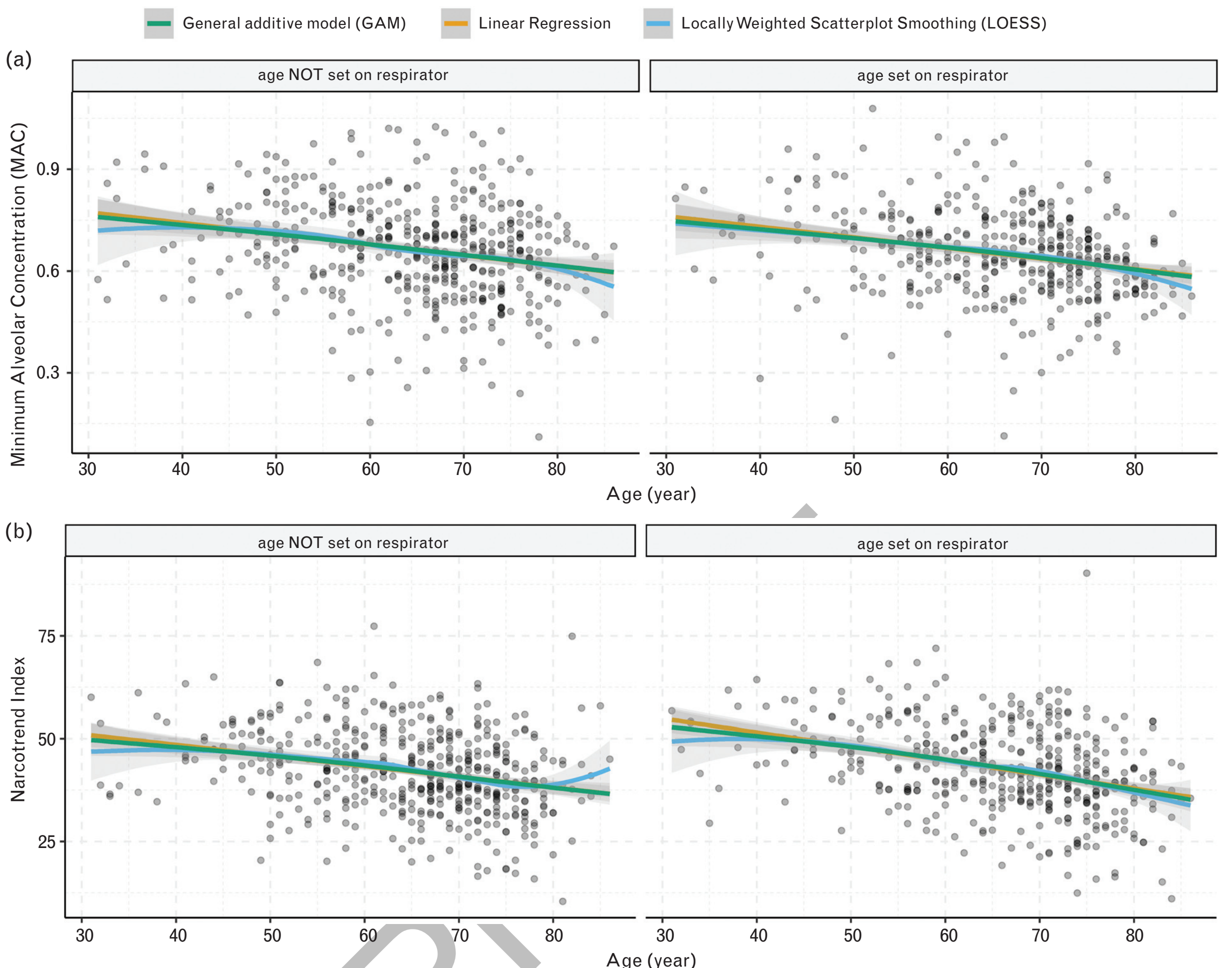
The nonlinear fitting methods (LOESS and GAM) only deviated from the linear regression fit at the extremes of age, where there were far fewer patients, suggesting that the estimated overall linear trend is robust across the three methods. We also found no significant correlation between patient age and percentage of missing Narcotrend Index values (Pearson's correlation $R = 0.032$, $P = 0.41$), indicating that older patients did not have more missing Narcotrend values than younger patients.

When comparing visually to the Ni *et al.* study, the Narcotrend index values seem to be slightly more widely dispersed than the BIS values (compare our Fig. 4 with their Fig. 2b). This effect has been more clearly shown in a very recent study by Obert *et al.*[42] that compared how five commercial indices change with age when given the same EEG signals. Of interest, in that study no decrease in Narcotrend index values was observed with age; this seemingly conflicting result is actually in harmony with our findings, as their age-adjusted MAC did not increase with age in that study.

Limitations

We recognise the following limitations concerning this study. First, the data studied are from a single centre and anaesthesia was with isoflurane only, limiting generalisability. Nonetheless, it is of interest to note how closely clinical practice in our European centre mirrors that reported in two studies completed in North America. Second, we do not have an even distribution of patients over age groups; this is usual in retrospective cardiac surgery studies where patients are more concentrated in the older age group. Furthermore, there are significantly more men in our database, as is characteristic of cardiac cohorts, but not of general surgery. Third, all of our data were recorded with EEG monitoring in place, and we therefore, cannot compare dosing changes with age when an EEG monitor was

Fig. 6 (a) The relationship between mean minimum alveolar concentration fraction given and age, as well as (b) Narcotrend Index and age stratified by setting the age on the anaesthetic machine, that is, displaying age-adjusted minimum alveolar concentration or not.



Relationships are visualised by linear regression (orange line), a generalised additive model (green line) and LOESS (blue line). Grey bands denote the 95% confidence intervals and grey dots represent individual patients.

not in place as in the Ni *et al.* study,[24] even though results were broadly similar (2.7% decrease in MAC when BIS was absent) in that study. We note that although clinicians could see the Narcotrend index in all patients and sometimes age-adjusted MAC (displayed in around half of our patients), this is no guarantee that those values were integrated into the clinical decision-making process.[43]

Table 2 **Results of the linear multivariable regression model regressing total Rocuronium dose over the operation, BMI, gender, and total dose of Sufentanil over the operation against age-adjusted minimum alveolar concentration**

	Linear regression on age-adjusted MAC		
Variable	**Beta**	**95% confidence interval**	***P***
Rocuronium (mg)	−0.00013	−0.00031 to 0.00005	0.2
BMI (kg m^{-2})	0.00175	−0.00051 to 0.00401	0.13
Gender (female)	−0.02553	−0.04995 to −0.00111	0.040
Sufentanil (μg kg^{-2} h^{-1})	0.03610	−0.01959 to 0.09179	0.2

MAC, minimum alveolar concentration.

Conclusion

Our analysis of patients undergoing cardiac surgery at a European centre shows a linear decrease of end-tidal MAC fraction of 3.2% per age-decade, strikingly consistent with the findings of Ni *et al.*[24] in the North American context but less than the 6% decrease expected from the literature.[4] In contrast, index values of our depth of sedation monitor, the Narcotrend Index, did not increase with age as seen with the BIS, but rather decreased with age, a direction of change consistent with the increasing age-adjusted MAC fraction with patient age. These relationships remained the same regardless of whether age-adjusted MAC was displayed on the anaesthetic machine. We caution that the 'paradox of age' may in part depend on choice of depth of sedation monitor.

Acknowledgements relating to this article

Assistance with the study: we thank Jeannie Wurz, medical editor, for editing this article and Monika Stucki, research nurse, for helping with data collection.

Financial support and sponsorship: The original study (Clinicaltrials.gov identifier: NCT02976584) was supported by the Bangerter-Rhyner Foundation and the Clinical Trials Unit of the University Hospital of Bern, University of Bern. This work was supported by the Department of Anaesthesiology and Pain Medicine, Bern University Hospital, University of Bern, Bern, Switzerland.

Conflicts of interest: none.

Presentation: none.

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