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# Autonomic cardiovascular modulation with three different anesthetic strategies during neurosurgical procedures.

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Abbreviated Title: autonomic modulation and anesthesia

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ABSTRACT

**Background:** Autonomic cardiovascular modulation during surgery might be affected by different anesthetic strategies. Aim of the present study was to assess autonomic control during three different anesthetic strategies in the course of neurosurgical procedures by the linear and non-linear analysis of two cardiovascular signals.

**Methods:** Heart rate (EKG-RR intervals) and systolic arterial pressure (SAP) signals were analyzed in 93 patients during elective neurosurgical procedures at fixed points: anesthetic induction, dura mater opening, first and second hour of surgery, dura mater and skin closure. Patients were randomly assigned to three anesthetic strategies: sevoflurane+fentanyl (S-F), sevoflurane+remifentanil (S-R) and propofol+remifentanil (P-R).

**Results:** All the three anesthetic strategies were characterized by a reduction of RR and SAP variability. A more active autonomic sympathetic modulation, as ratio of low to high frequency spectral components of RR variability (LF/HF), was present in the P-R group vs. S-R group. This is confirmed by non-linear symbolic analysis of RR series and SAP variability analysis. In addition, an increased parasympathetic modulation was suggested by symbolic analysis of RR series during the second hour of surgery in S-F group.

**Conclusions:** Despite an important reduction of cardiovascular signal variability, the analysis of RR and SAP signals were capable to detect information about autonomic control during anesthesia. Symbolic analysis (non-linear) seems to be able to highlight the differences of both the sympathetic (slow) and vagal (fast) modulation among anesthetics, while spectral analysis (linear) underlines the same differences but only in terms of balance between the two neural control systems.

Key words: anesthesia, autonomic nervous system, heart rate variability, neurosurgery

## INTRODUCTION

In 1958, Heymans and Neil [1] described a blunted but not abolished autonomic modulation of cardiovascular system during anesthesia, confirmed in later studies [2,3]. Analysis of cardiovascular signal variability is considered a quantitative method to assess cardiovascular autonomic control in awake subjects [4]. Differently, discordant results regarding the usefulness of non-invasive autonomic indices extracted from cardiovascular signals during anesthesia were reported [5-7]. Undoubtedly, cardiovascular signal variability is markedly reduced during anesthesia compared to an awake condition [8].

Information about autonomic modulation of cardiovascular system during anesthesia could help to choose the best anesthetic strategy, tailored for the single patient during a specific procedure. Moreover, a better knowing of cardiovascular oscillations could open new prospects to continuously monitor autonomic activity during surgery and to correct in real time autonomic imbalance, before evident changes in heart rate and arterial pressure become manifest.

Currently, propofol-opioid and sevoflurane-opioid combinations are the most frequently anesthetics for neurosurgical procedures. Clinically, limited data are available to support a clear superiority for either treatment. In a cohort of patients enrolled in the NeuroMorfeo trial [9], a multicentre, randomized, open-label, pragmatic equivalence design trial aimed to test equivalence for inhalation and intravenous anesthesia maintenance techniques in patients undergoing elective intracranial neurosurgery, we decided to assess cardiovascular autonomic modulation. For the first time, linear and non-linear indices derived from variability of two cardiovascular signals were utilized to recognize autonomic control during different anesthetic strategies. The primary aim of this study is to evaluate if different anesthetic strategies provide a different impact on cardiovascular autonomic modulation.

## MATERIALS AND METHODS

Ninety-three patients were recorded during surgical procedures in 5/14 centres involved in the "NeuroMorfeo" study (Fig.1). The five centers have been selected as hospital where a continuous computerized data acquisition during surgery was possible. The NeuroMorfeo trial is registered on Eudract (12.10.2007, 2007-005279-32) and on AIFA register (FARM6FKJKK). The NeuroMorfeo trial enrolled patients aged 18-75 years, scheduled for elective supratentorial intracranial surgery under general anesthesia, meeting all the following criteria: ASA physical status classification from II to III; normal preoperative level of consciousness, i.e. Glasgow Coma Scale 15, and no clinical and CT signs of intracranial hypertension.

Three anesthetic strategies, two balanced, sevoflurane+fentanyl (S-F) and sevoflurane+remifentanil (S-R) and one intravenous, propofol+remifentanil (P-R), were randomly assigned. The protocol [9] and the main results of the trial have been recently published [10] and protocol details are in a open access journal. The study groups and dosages reflect the clinical practice of the participating centers and have been defined during preparatory meetings with all the investigators.

Before induction, all patients were premedicated with IV midazolam 5 mg. Patients were induced with propofol 2–3 mg/kg IV and cisatracurium 0.1–0.2 mg/kg IV, plus additional fentanyl 2–4 µg/kg IV for patients randomized to S-F and remifentanil 0.25 µg/kg/min IV infused for 3 minutes before induction for patients randomized to S-R or P-R.

All patients were mechanically ventilated using a closed breathing system to achieve an end-tidal carbon dioxide of 30–35 mmHg. No local anesthesia was permitted. Anesthesia was maintained as follows:

- S-F: sevoflurane 0.75–1.25 MAC range and fentanyl 2–3 µg/kg/hr or 0.7 µg/kg boluses;
- S-R: sevoflurane 0.75–1.25 MAC range and remifentanil 0.05–0.25 µg/kg/min reduced to 0.05–0.1 µg/kg/min after dural opening;

• P-R: propofol continuously infused at 10 mg/kg/h for 10 minutes, reduced to 8 mg/kg/h for 10 minutes, and then reduced to 6 mg/kg/h for the remainder of the procedure; remifentanil infused at 0.05–0.25 µg/kg/min, reduced to 0.05–0.1 µg/kg/min after dural opening.

Supplemental treatment with fentanyl for S-F or remifentanil for S-R or P-R groups were permitted immediately prior to scalp incision, as needed, as determined by the surgical team. All patients were paralyzed during surgery with cisatracurium 0.1 mg/kg/h, which was discontinued once the bone flap was secured. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1 mg. Sevoflurane and propofol infusions were reduced once the bone flap was secured and stopped at skin dressing. Fentanyl was stopped at skin dressing and remifentanil reduced at skin dressing by 30% every 3–4 minutes. Analgesia was started before bone flap repositioning with paracetamol (1 g) and, in remifentanil groups, morphine 0.03–0.1 mg/kg IV. Post-operative analgesia was permitted using morphine or fentanyl in the recovery room and stepwise administration of paracetamol, ketoprofen or morphine during the first 24 hours after surgery.

During anesthesia all patients were continuously monitored, as minimal standard, with EKG, invasive arterial pressure, $SpO_2$, $EtCO_2$, and temperature.

Heart rate (EKG-RR intervals) and systolic pressure (SAP) signals, for having comparable time points, were recorded at standardized time points:

1. Anesthetic induction (AI),
2. Dura mater opening (DMO), i.e. start of the intracranial procedure,
3. End of first hour of surgery (S1), i.e. stable anesthesia plan,
4. End of second hour of surgery (S2), i.e. stable anesthesia plan,
5. Dura mater closure (DMC), i.e. end of the intracranial procedure,
6. Skin closure (SC), i.e. end of surgery.

RR or SAP series were considered analyzable when were artifact-free and both signals were continuously recordable for at least 250 beats.

EKG and SAP signals were captured in operating theatre connecting the OR monitoring system with a laptop (Latitude D600, Dell, US) through a computer acquisition system (LabView, National Instruments 2000, Texas, USA) in conjunction with a data acquisition card (National instruments DAQ Card 6036E), all provided to each of the five participating centres. Sampling rate was 250 Hz. Traces were recorded for 250 beats during each phase of the protocol, using a computerized procedure made ad hoc by BT. Frequency domain analyses of cardiovascular signals were performed with an autoregressive algorithm previously described [4]. Total power (variance) and two spectral components were considered: low frequency (LF), from 0.04 to 0.15 Hz; and high frequency (HF), from 0.15 to 0.50 Hz. Following data acquisition, the LF/HF ratio was calculated over RR variability, as a marker of sympatho-vagal balance.

A normalized complexity index (NCI) based on conditional entropy, a non-linear measure of complexity of RR interval series [11], was calculated (the larger NCI, the more irregular and unpredictable the signal). Using NCI, complexity of a cardiovascular signal was measured by evaluating the amount of information carried by the most recent sample of the series when an optimized number of previous values were given [12].

Symbolic analysis was fully described and validated previously [13-15]. Briefly, the full range of each RR sequences was uniformly spread on 6 levels (from 0 to 5), and patterns of length L=3 beats were constructed. Therefore, each subject and each experimental condition had its own range of RR intervals. All possible patterns (i.e., 216) were grouped without any loss into 4 families referred to as:

- Patterns with no variation (0V; i.e., all 3 symbols were equal),
- Patterns with 1 variation (1V; i.e., 2 consequent symbols were equal and the remaining symbol was different),

- Patterns with 2 variations with one sign (2LV; i.e., patterns with two like variations, the second and the third symbol change with respect to the previous one and the changes have the same sign),
- 2 variations with opposite signs (2UV; i.e., patterns with two unlike variations, the second and the third symbol change with respect to the previous one and the changes have opposite sign).

Previous studies showed that the percentage of 0V patterns increased (0V%) in experimental conditions characterized by a prevalent sympathetic modulation, while that of 2UV patterns (2UV%) augmented when parasympathetic control was dominant [13-15]. The percentages of 1V and 2LV patterns (i.e. 1V% and 2LV%) were monitored as well.

Baroreflex sensitivity was estimated over spontaneous RR and SAP variability series in the LF band as the square root of the ratio of the LF power of RR series to that of the SAP one [16]. The index was indicated as $_{LF}$ in the following and expressed in ms/mmHg. Blood and urine samples for evaluating stress biomarkers (cortisol and catecholamines) have been collected 1 hour after the end of neurosurgery procedure, as previously described [17].

Analyses were performed blindly, without knowledge of study group assignments.

The Institutional Ethical Review Boards of the involved Hospitals approved the study. All patients gave written informed consent.

*Statistical Analysis*

Two-way repeated measures analysis of variance, one factor repetition, and multiple comparison procedure (ANOVA and Holm-Sidak method; SigmaStat 3.5, Systat Software, Inc., Point Richmond, CA USA) were used. Qualitative data were analyzed using $\chi^2$ test. Data in the tables and figures are presented as mean ± standard deviation (SD). Two-sided p-value $< 0.05$ was considered to be statistically significant.

RESULTS

The main characteristics of the patients were comparable in the three groups (i.e. S-F, S-R and P-R) and the number of major intraoperative episodes was similar (Tab.1).

Out of 93 patients enrolled, 86 patients had ECG and arterial pressure analyzable at least for five phases of protocol. Seven patients did not have recording of RR series or SAP analyzable (artifact-free > 250 beats) in the five phases. Out of 86 patients considered for the analysis, 33 were allocated to S-F, 24 to S-R, and 29 to P-R (Fig.1).

RR mean, RR variance and LF/HF ratio are shown in Fig.2. RR mean tended to decrease during anesthesia, independently of the anesthetic strategy. However, RR mean was significantly decreased only during SC compared to AI. No significant differences were found among anesthetic strategies. RR variance was reduced significantly with respect to AI during the other protocol phases (i.e. DMO, S1, S2, DMC and SC). This trend was found in all anesthetic strategies, without significant differences among anesthetic strategies. LF/HF ratio remained unchanged during different protocol phases. P-R group showed LF/HF values significantly higher than in S-F and S-R groups.

NCI (normalized complexity index) was 0.58±0.02, 0.70±0.01, 0.68±0.01, 0.67±0.02, 0.67±0.01, 0.61±0.01 during AI, DMO, S1, S2, DMC and SC and significantly increased with respect to AI during DMO, S1, S2 and DMC, while decreased significantly from DMO to SC. When NCI values were pooled together in each group independently of the protocol phase, NCI was similar in S-F, S-R and P-R groups (0.66±0.10, 0.66±0.13, 0.62±0.11 in S-F, S-R and P-R groups respectively).

Results of symbolic analysis are shown in Fig.3. 0V% remained unmodified while varying the protocol phases with exception of the significant decrease observable during S1 with respect to AI in P-R group. When 0V% values were pooled together in each group independently of the protocol phase, 0V% was significantly increased in P-R group compared to S-F and S-R ones (i.e. 29.0±8.1, 28.9±9.8, and 35.9±8.6 % in S-F, S-R and P-R groups respectively; $p>0.05$). 1V% was similar in all the protocol

phases in all the groups. 1V% did not exhibit any difference among groups. 2LV% significantly increased during DMO, S1 and S2 with respect to AI in S-F group, while it was not affected by protocol phases in S-R and P-R groups. 2LV% did not show any difference among groups. 2UV% significantly increased during S2 with respect to AI in S-F group and with respect to SC in S-R group. 2UV% was significantly lower in P-R group than in S-R one.

SAP mean, SAP variance, LF and HF powers are shown in Fig.4. SAP mean was stable during the protocol phases and unaffected by the anesthetic strategies. SAP variance was reduced significantly with respect to AI during all the protocol phases (i.e. DMO, S1, S2, DMC and SC). This trend was found in S-F and P-R groups. Conversely SAP variance remained unchanged in S-R group. When SAP variance values were pooled together in each group, SAP variance was significantly larger in P-R group than in S-R one (15.5±12,1, 11.8±15.1, 21.6±13.7 $mmHg^2$ in S-F, S-R and P-R groups respectively). LF power of SAP was constant while varying the protocol phases in all the groups. However, when LF power values were pooled together in each group, they were significantly larger in P-R groups than in S-F and S-R ones (0.89±2.24, 0.55±2.63, and 2.55±2.26 $mmHg^2$ in S-F, S-R and P-R groups respectively). HF power was independent of the protocol phases in all the groups. HF power of SAP during S2 in P-R group was larger than that in S-F and S-R groups (5.9±4.0 ,4.5±4.0, and 11.6±9.7 mmHg2 in S-F, S-R and P-R groups respectively).

The $_{LF}$ (index of baroreflex sensitivity) was not affected by the protocol phases in all the groups. When $_{LF}$ values were pooled together in each group independently of the protocol phase, $_{LF}$ was similar in S-F, S-R and P-R groups (16.4±46.5, 20.0±74.8, 12.3±18.0 ms/mmHg in S-F, S-R and P-R groups respectively).

Noticeable, considering two phases, open and closed dura, in which depth of anesthesia must be ensured, all the three cardiovascular oscillation variables considered signs of sympathetic modulation, LF/HF, 0V and LF power of SAP were higher in P-R than in S-R group (Figures 2,3 and 4)

Plasma concentration of noradrenaline, adrenaline and dopamine measured 1 hour after the end of neurosurgery procedure were characterized by a high dispersion of values without significant differences among anesthetic strategies. Conversely, cortisol measured 1 hour after the end of neurosurgery was lower in P-R group than in S-R and P-R ones (Table 2).

## DISCUSSION

To evaluate autonomic tone in anesthetized patients, the variability of cardiovascular signals was assessed in different surgical contexts [18]. Even if the interpretations and the usefulness of the results of these analyses are discordant [5-7]. The accounting for linear and non-linear analyses of variability of two cardiovascular signals during different anesthetic strategies were the novel contribution of the present study. These analyses can potentially provide useful information about the course of anesthesia, according to the observations of blunted, but not abolished, autonomic cardiovascular control during anesthesia [1-3].

Our present results confirm that the variability of RR-intervals and SAP were markedly depressed during neurosurgerical procedures. Nevertheless, the analysis of oscillations of cardiovascular signals was able to detect some differences among surgery phases and among the three distinct anesthetic strategies. In particular, LF/HF ratio and 0V% assessed over RR series, and LF power over SAP series were found higher during intraoperative phases in P-R group with respect to the other two groups. These results of linear and non-linear analysis can be interpreted as signs of a more active autonomic sympathetic modulation in P-R anesthetic group during surgery. The trend toward a minor number of hypotensive episodes in this group can be interpreted in the same way. A relation between hypotensive episodes during anesthesia and changes in LF/HF assessed over RR series were previously described during spinal anesthesia in pregnant women scheduled for elective cesarean [19]. Different effects of propofol and servofluorane, with a minor decrease of LF power assessed over RR series during propofol, were detected in elective oral surgery [20], as well as higher values of LF/HF ratio calculated over RR series

with midazolam-propofol compared with propofol in the same type of surgery [21]. Two different readings of these data are achievable. First, the analgesia was less complete with P-R strategy, pain was present, and sympathetic activity was consequently higher [22,23]. Second, these data were expression of a less depressed sympathetic control system in P-R group, with an equal analgesic efficacy of the anesthesia. The lower postoperative value of plasmatic cortisol in P-R group seems to strengthen this second hypothesis [24].

The increased presence of fast RR changes as evaluated in terms of increase of 2UV% in S-R respect to P-R group was, in our opinion, equally interesting. Indeed, 2UV% is considered an index of parasympathetic modulation [13-15]. In non-physiological conditions, like anesthesia, symbolic analysis (non-linear analysis) seems more suitable than spectral analysis (linear analysis) [25] to measure agonist and antagonist interactions of parasympathetic and sympathetic modulation and more capable to deal with nonlinearities of cardiovascular control described during anesthesia with sevoflurane [26].

In our setting, NCI increased from AI to DMO in a opposite direction of RR variance and independently of the anesthetic treatment. From DMO to SC a trend of NCI toward a reduction was detectable. During sevoflurane induction of neurosurgical anesthesia low value of entropy compared to awake were reported [27], while during anesthesia a reduction of entropy was described with propofol, but not with sevoflurane [20].

In our study a spontaneous baroreflex index ($_{LF}$) did not detect differences in baroreflex gain during the different surgical phases studied and among the three anesthetic strategies randomly assigned. This disappointing result might suggest that the use of spontaneous RR and SAP variations to infer baroreflex sensitivity cannot surrogate during anesthesia the traditional method based on the administration of a vasoactive drug [28]. Recently results pointed out the necessity of accounting for respiratory signal in order to obtain reliable $_{LF}$ [29].

As limitation of the study, preoperative recordings of cardiovascular signals for comparisons with intraoperative data of the same subject were not collected. In addition, a follow-up of postoperative cardiac events to assess the role of heart rate variability in risk stratification for adverse events was not carried out.

The analysis of RR-intervals and SAP seems capable to distinguish different autonomic patterns during the subsequent phases of neurosurgery and among three anesthetic strategies. A reduced presence of slow oscillation of cardiovascular signals was detectable during surgery in S-F and S-R groups compared to intravenous P-R treatment. On the other hand, during surgery and with S-F treatment fast oscillations of RR-intervals were more present. Symbolic analysis (non-linear) seems to be able to highlight the differences of both the sympathetic (slow) and vagal (fast) modulation among anesthetics, while spectral analysis (linear) underlines the same differences but only in terms of balance between the two neural control systems. A better understanding of cardiovascular oscillations during surgery could open new possibilities to monitor continuously the state of the patient and to correct in real time autonomic imbalances, before the occurrence of evident changes in heart rate and arterial pressure become manifest. A limitation of the study is its pragmatic design and the fact that we didn't use any system for comparing the depth of anesthesia in the different groups. Infact, defining the drugs' dosing in the three groups, we surveyed the 14 participating centers and we predefined the dosing that are used in clinical practice. Moreover, we decided to avoid TCI and EEG-derived monitoring, not routinely used in most of the centres. The depth of anesthesia of the three techniques was clinically equivalent.

Key Messages:

1 During anesthesia the variability of cardiovascular signals were markedly depressed. Nevertheless, different analysis of the oscillations of two cardiovascular signals during three different anesthetic strategies showed coherent and distinctive representations of autonomic control.

2 Signs of autonomic sympathetic modulation of cardiovascular system with propofol+remifentanil (P-R) anesthesia compared with sevoflurane+remifentanil (S-R) anesthesia were more recognizable.

3 Symbolic analysis (non-linear) of RR variability seem able to find more features of autonomic modulation during general anesthesia than spectral analysis (linear).

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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**Figure legends**

Figure 1

Enrolment and randomization of the study participants.

Figure 2

Linear indices of (EKG) RR-intervals analysis. S-F sevoflurane+fentanyl; S-R sevoflurane+remifentanil; P-R propofol+remifentanil. Protocol phases in the abscissas: A (AI) anesthetic induction, O (DMO) dura madre opening, 1° (S1) end of first hour of surgery, 2° (S2) end of second hour of surgery, C (DMC) dura madre closure, S (SC) skin closure. Data are expressed as mean and SD. * $p<0.05$; ** $p<0.01$

Figure 3

Symbolic patterns of (EKG) RR-intervals analysis. S-F sevoflurane+fentanyl; S-R sevoflurane+remifentanil; P-R propofol+remifentanil. Protocol phases in the abscissas: A (AI) anesthetic induction, O (DMO) dura madre opening, 1° (S1) end of first hour of surgery, 2° (S2) end of second hour of surgery, C (DMC) dura madre closure, S (SC) skin closure. Data are expressed as mean and SD. * $p<0.05$

Figure 4

Linear indices of SAP analysis. S-F sevoflurane+fentanyl; S-R sevoflurane+remifentanil; P-R propofol+remifentanil. Protocol phases in the abscissas: A (AI) anesthetic induction, O (DMO) dura madre opening, 1° (S1) end of first hour of surgery, 2° (S2) end of second hour of surgery, C (DMC) dura madre closure, S (SC) skin closure. Data are expressed as mean and SD. * $p<0.05$

**Table 1 -** Preoperative characteristics of patients

**Table 2 –** Postoperative markers

**Table 1 -** Preoperative characteristics of patients

| ***Group of anesthetic strategy*** | **S-F** | **S-R** | **P-R** |
|---|---|---|---|
| No. of patients | 33 | 24 | 29 |
| Age – yr (mean±SD) | 59±12 | 56±13 | 55±14 |
| Male sex – no. (%) | 13 (39.3)* | 15(62.5) | 20 (68.9) |
| Weight – kg (mean±SD) | 76±12 | 73±17 | 72±13 |
| Height – cm (mean±SD) | 169±9 | 167±8 | 168±9 |
| Arterial hypertension – no. (%) | 11 (33.3) | 13 (54.1) | 12 (41.3) |
| Diabetes – no. (%) | 4 (12.1) | 2 (8.3) | 3 (10.3) |
| SBP - mmHg (mean±SD) | 131±14 | 130±21 | 125±13 |
| DBP - mmHg (mean±SD) | 78±8 | 78±9 | 77±10 |
| HR - beats/min (mean±SD) | 73±14 | 70±9 | 72±16 |
| ***Number of intraoperative episodes*** | | | |
| Hypotension MAP<50 mmHg (%) | 9 (27.3) | 9 (37.5) | 6 (20.7) |
| Hypertension MAP>95mmHg (%) | 22 (66.7) | 16 (66.7) | 12 (41.4) |
| Bradycardia FC<50 bpm (%) | 4 (12.1) | 8 (33.3) | 7 (24.1) |
| Tachycardia FC > 95 bpm (%) | 1 (3.0) | 2 (8.3) | 0 (0) |
| Osmotic drugs for swelling(%) | 5 (15.2) | 5 (20.8) | 4 (13.8) |
| Hyperventilation (End-Tidal $CO_2$ paCO2 < 30 mmHg) (%) | 9 (27.3) | 9 (37.5) | 8 (27.6) |

S-F sevoflurane+fentanyl; S-R sevoflurane+remifentanil; P-R propofol+remifentanil.

*p=0.05

**Table 2 –** Postoperative markers

| ***Postoperative markers*** | **S-F** | **S-R** | **P-R** |
|---|---|---|---|
| noradrenaline – ng/ml | 25.69±25.31 | 14.10±8.08 | 12.69±11.56 |
| adrenaline – ng/ml | 17.23±15.25 | 13.47±9.62 | 10.22±8.01 |
| dopamine – ng/ml | 124.45±132.76 | 310.02±828.99 | 151.35±549.03 |
| cortisol – nmol/l | 306.80±362.57 | 209.46±260.87 | 68.55±119.14* |

Data are presented as mean±SD. S-F sevoflurane+fentanyl; S-R sevoflurane+remifentanil; P-R propofol+remifentanil. S-F vs P-R *p< 0.01