Peer-reviewed version available at *Entropy* **2020**, *22*, 356; doi:10.3390/e22030356

Article

Impact of General Anaesthesia - guided by State Entropy (SE) and Response Entropy (RE) on Perioperative Stability in Elective Laparoscopic Cholecystectomy Patients. A Prospective Observational Randomized Monocentric Study

Anca Raluca Dinu [1], Alexandru Florin Rogobete [1,2,3,*], Sonia Elena Popovici [2,3], Ovidiu Horea Bedreag [1,2,3,#], Marius Papurica [1,2,3,#], Corina Maria Dumbuleu [2,3], Raluca Ramona Velovan [2,3], Daiana Toma [2,3], Corina Maria Georgescu [2,3], Lavinia Ioana Trache [2,3], Claudiu Barsac [2,3], Loredana Luca [2,3], Bettina Buzzi [2,3], Andra Maghiar [2,3], Mihai Alexandru Sandesc [1,*], Samir Rimawi [2,3], Madalin Marian Vaduva [2,3], Lavinia Melania Bratu [1], Paul Manuel Luminosu [2,3], and Dorel Sandesc [1,2,3#]

[1] Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy, Timisoara 300041, Romania; anca.dinu.umft@gmail.com (A.R.D.), alexandru.rogobete@umft.ro (A.F.R.), bedreag.ovidiu@umft.ro (O.H.B.), marius.papurica@gmail.com (M.P.), msandesc19@gmail.com (M.S.), lavi.ceuta@gmail.com (L.M.B.), dsandescumft@gmail.com (D.S.); bettynabuzzi@yahoo.com (B.B.), raluca_velovann@yahoo.com (R.R.V.),

[2] Clinic of Anaesthesia and Intensive Care, Emergency County Hospital "Pius Brinzeu", Timisoara 325100, Romania; popovici.sonia@yahoo.com (S.E.P.), loredana_ati@yahoo.com (L.L.), rimawi.samir@gmail.com (R.S.), corinageorgescu28.85@yahoo.com (C.M.G.), lavinia_trache@yahoo.com (L.I.T.), vaduvamadalin14@gmail.com (M.M.V.),

[3] Department of Clinical Research and Medical Education, Romanian Society of Anaesthesia and Intensive Care (SRATI), Timisoara 325100, Romania

* Correspondence: alexandru.rogobete@umft.ro (A.F.R.) and msandesc19@gmail.com (M.S.); Tel.: +40 728 001 971 (A.F.R.)

# M.P., O.H.B. and D.S. have equal contributions to this paper.

Abstract:

Study background and aims: Laparoscopic cholecystectomy is one of the most frequently performed interventions in departments of general surgery. One of the most important aims in achieving perioperative stability of these patients is diminishing the impact of general anesthesia on the hemodynamic stability and the optimization of anesthetic drug doses based on the individual clinical profile of each patient. The objective of this study is the evaluation of the impact monitoring the depth of anesthesia through Entropy (state entropy – SE and response entropy -RE) has on the hemodynamic stability and on the doses of volatile anesthetic.

Material and Methods: This is a prospective, observational, randomized, monocentric study carried out between January 2019 and December 2019 in the Clinic of Anesthesia and Intensive Care from the "Pius Brînzeu" Emergency County Hospital in Timișoara, Romania. The patients included in the study were divided in two study groups; patients in Group A (target group) received multimodal monitoring that included monitoring of standard parameters and of Entropy (SE and RE), while patients in Group B (control group) only received standard monitoring. Anesthetic dose in group A were optimized to achieve a target entropy of 40-60.

Results: 68 patients met the inclusion criteria and were allocated to one of the two study groups, Group A (N=43) and Group B (N=25). There were no statistically significant differences identified between the two groups for both demographical and clinical data ($p>0.05$). Statistically significant

differences have been identified for the number of hypotensive episodes (p = 0.011, 95% CI 0.1851 to 0.7042) and for the number of episodes of bradycardia (p < 0.0001, 95% CI 0.3296 to 0.7923). Moreover, there was a significant difference in the Sevoflurane consumption between the two study groups (p = 0.0498, 95% CI -0.3942 to 0.9047).

Conclusions: The implementation of the multimodal monitoring protocol that includes the standard parameters and the measurement of Entropy for determining the depth of anesthesia (SE and RE) lead to a considerable improvement in perioperative hemodynamic stability. Optimizing the doses of anesthetic drugs based on the individual clinical profile of each patient leads to a considerable decrease in drug consumption as well as to a lower incidence of hemodynamic side-effects.

Keywords: state entropy; response entropy; general anaesthesia; patient safety; recovery.

1. Introduction

Globally, laparoscopic cholecystectomy is considered to be the most frequently performed intervention in the field of general and abdominal surgery [1]. During the last years the incidence of pathological processes of the gall-bladder has increased with over 50% in certain regions [1]. Therefore, the number of patients admitted for specific laparoscopic interventions has increased significantly, leading to an increase in the number of postoperative complications. These reflect both in the clinical evolution, with increased length of stay and decreased patient satisfaction, as well as in the economical segment of healthcare [1,2].

A series of recent guidelines recommend multimodal monitoring of general anesthesia for increasing patient safety. The minimal mandatory monitoring includes pulse oximetry, electrocardiography, non-invasive monitoring of arterial blood pressure (NIBP), capnography ($EtCO_2$), fraction of inspired oxygen (FiO_2), fraction of expired oxygen (FeO_2), anesthetic gas concentration, airway pressure, and temperature. Recent recommendations focus on the introduction in the daily routine of certain additional parameters such as degree of hypnosis monitoring (depth of anesthesia), the evaluation of nociception-antinociception balance, and neuromuscular transmission monitoring. Depending on the clinical profile of each patient, advanced monitoring can be further extended by introducing special parameters for the evaluation of hemodynamic status.

However, a high number of general anesthetics are carried out with no advance monitoring, based only on clinical signs such as lacrimation, sweating, changes in heart rate and blood pressure, or major ventilatory imbalances that could be directly correlated with the degree of hypnosis. Another parameter routinely used but questioned in the last years is the minimum alveolar concentration (MAC). Based on the literature researchers have concluded that MAC cannot guarantee a balanced anesthesia as it can vary based on different factors such as the type of surgery, patient comorbidities or age.

The most common techniques used for monitoring the degree of hypnosis are systems based on EEG-signal interpretation [3–6]. One of the most widely studied parameters in this area is the bispectral index (BIS) and the Entropy – which further includes State Entropy (SE) and Response Entropy (RE). Even with them available, at the time being there is no gold standard for monitoring the degree of hypnosis in general anesthesia. In order to integrate technology in clinical practice it is preferred to apply the concept of multimodal monitoring that includes both the monitoring of the degree of hypnosis, as well as the classical hemodynamic and respiratory variables.

The main objective of this study was to analyze the statistical and clinical impact of a multimodal monitoring protocol that includes classical monitoring parameters as well as depth of anesthesia

monitoring through Entropy. Secondary objectives are analyzing the impact on drug consumption and analyzing the general clinical prognosis of these patients.

2. Materials and Methods

2.1. Study population

This is a prospective, observational, randomized study that was carried out in the Clinic for Anesthesia and Intensive Care of the "Pius Brînzeu" Emergency County Hospital, Timișoara, Romania between January 2019 and December 2019. The study is part of a larger group of clinical study of the Department for Research and Medical Education of the Romanian Society of Anesthesia and Intensive Care in Romania (www.srati.ro). The identification code in the ClinicalTrials.gov data base is NCT03210077. This study was approved by the Ethics Committee of the institution and all the procedures respect the Helsinki Declaration for clinical studies and patient safety.

The included patients were randomized in two study groups; the multimodal monitoring protocol was implemented in patient Group A or the target group (heart rate, HR, bpm; blood pressure, BP, mmHg; peripheral oxygen saturation, SpO_2, %; capnography, $EtCO_2$, mmHg; State Entropy, SE; Response Entropy, RE; inspired oxygen fraction, FiO_2; minimum alveolar concentration, MAC); in Group B or the control group general anesthesia was guided based on standard procedure (heart rate, HR, bpm; blood pressure, BP, mmHg; peripheral oxygen saturation, SpO_2, %; capnography, $EtCO_2$, mmHg; inspired oxygen fraction, FiO_2; minimum alveolar concentration, MAC). Based on the study protocol the patients' inclusion criteria were as follows: age – over 18, gender - male and female, surgical procedure – laparoscopic cholecystectomy, inhalational general anesthesia with Sevoflurane. The exclusion criteria were: pregnancy, septic shock, massive hemorrhage, ketamine administration, and total intravenous anesthesia (TIVA). Patient allocation to the study group was randomized using online software (http://www.randomization.com).

2.2. Measurements and data management

Study data was processed from the prior approved monitoring form. The data were filed electronically by the ""Data Officer", later being de-identified and secured under a password in the study data base. The study data base included demographical and clinical data of all patients in the study, as well as values of the monitored parameters based on protocol, as follows: individual patient code, gender, age, ASA score, type of surgery, surgery duration, RE and SE values, heart rate, systolic blood pressure, peripheral oxygen concentration, minimum alveolar concentration, gas flow, inspired oxygen fraction, number of hemodynamic events – hypertension, hypotension, tachycardia, bradycardia. Doses of used anesthetic drugs have also been recorded for Fentanyl, Propofol, Rocuronium, Sevoflurane, vasopressor drugs and maintenance fluids given in the perioperative period. Regarding the hemodynamic parameters data recording was carried out based on the following scheme: time of start – before orotracheal intubation (M0), followed by continuous recordings at every 15 minutes (M15, M30, […]), with the last recording at ± 5 minutes before extubation (Mext).

For the characteristic hemodynamic events these were considered as follows: hypotension if systolic blood pressure dropped under 70mmHg, hypertension if systolic blood pressure increased with over 20% compared to the start value; bradycardia for heart rate under 45 bpm, tachycardia for heart rate over 100 bpm. For study Group A general anesthesia was optimized based on the Entropy values which was maintained in the 40-60 interval based on current guidelines. In study Group B general anesthesia was guided based on classical schemes of drug dosing and optimization.

2.3. General Anaesthesia and Monitoring

After the admissison in the operating room (OR) all patients were monitored using a standard monitor (Carescape B650, GE Healthcare, Helsinki, Finland). SE and RE were monitored using the same device with the Entropy module attached (E-Entropy Module, GE Healthcare, Helsinki, Finland). Entropy sensors were places on the forehead of patients in Group A based on the producer's guidelines. During induction all patients recieved the same drugs based on local protocols. Mechanical ventilation and hypnosis was achieved through continuous administration of Sevoflurane by using the same anesthesia machine for all patients (both in Group A and in Group B) (Avance CS2, GE Healthcare, Chicago, IL, US).

2.4. Statistical analysis

All clinical data were registered in the electronic study data base by the "Data Officer". The electronic GraphPad 7 (Graphad Software Inc., CA, US) was used for the statistical analysis. Regarding the statistical methodology for quantitative values we calculated the mean and standard deviation, while for qualitative values we calculated frequency and percentage. The confidence interval 95% (95%CI) was also presented as an argument for statistical differences. The Student t test (normal distribution) and the Mann-Whitney U test (non-normal distribution) were applied for comparison between numerical values. Multiple comparisons were carried out using the one-way ANOVA test. Statistically significant differences were considered for a $p<0.05$.

3. Results

3.1. Clinical and demographical characteristics

Between January 2019 and December 2019 68 patients have been identified as eligible for the study based on the inclusion and exclusion criteria. The total number of patients presenting with the studied pathology was N=105 but a number of these were excluded from the study protocol. After applying the randomization protocol 43 patients were allocated to Group A and 25 patients to Group B. No particular events have been recorded in either of these groups that could have led to the exclusion of certain patients from the study (Figure 1).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

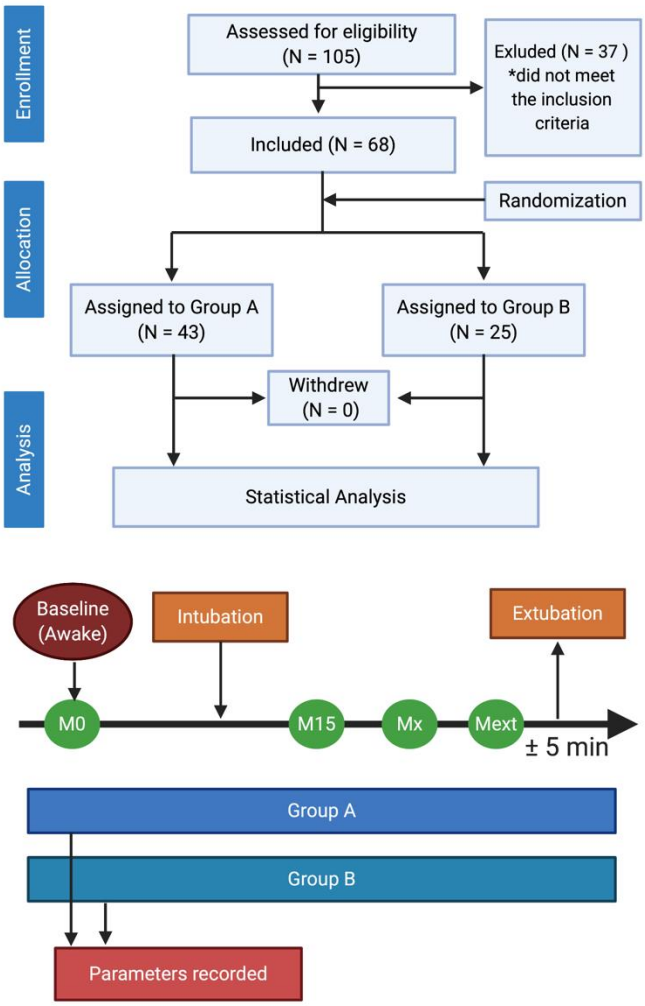

Figure 1. Study flowchart and data processing methodology

For further statistical evaluation we first compared demographic and clinical data (Table 1) of patients in Group A and Group B, with no statistically significant differences. The Chi square-test with 1 d.f. was used for analyzing the gender distribution. The Student t-test (two-tailed, unpaired) was used for the comparison of the other values. The Confidence Interval (95%) was also presented for all the analyzed characteristics.

Table 1. Clinical and demographical characteristics of the study groups

Characteristic	Group A (N=43)	Group B (N=25)	95% Confidence Interval	Statistical p value
Age, years, mean ± SD	51 ± 16.51	52.20 ± 13.79	-6.620 to 9.020	> 0.05
Weight, kg, mean ± SD	87 ± 2.71	91 ± 1.99	-5.445 to 7.012	> 0.05
Gender, M, N (%)	7 (16.28)	6 (24)	-10.8233% to 28.7947 %	> 0.05

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

ASA Score, I, N (%)	10 (23)	3 (12)	-0.5716% to 27.4520%	> 0.05
ASA Score, II, N (%)	24 (56)	17 (68)	-11.9231% to 32.8672%	> 0.05
ASA Score, III, N (%)	6 (14)	5 (20)	-11.3628% to 26.5172%	> 0.05
HR at M0, bpm, mean ± SD	78.48 ± 13.87	75.32 ± 14.28	-10.46 to 3.616	> 0.05
SAB at M0, bpm, mean ± SD	136.5 ± 22.47	134 ± 17.51	-12.97 to 7.917	> 0.05
	SD, standard deviation; M, male; N, number of patients; HR, heart rate; SAB, systolic blood pressure; M0, time before intubation/moment 0; p, statistically significant for $p < 0.05$			

3.2. State Entropy and Response Entropy expression

After induction of general anesthesia in Group A we observed a decrease in the value of both SE and RE. At Mo the mean values for SE and RE were 91.37 vs. 97.47 (mean difference -6.100). After orotracheal intubation and stabilization of the degree of hypnosis the mean values for SE and RE were becoming progressively equal (M15: 48.14 vs. 50.07, mean difference -1.930; M30: 48.56 vs. 48.60, mean difference -0.0400). Interestingly, after reducing the Sevoflurane concentration and the degree of hypnosis the difference between the mean SE and RE increases to the initial value. Following this trend, before extubation, at Mext, the mean values for SE and RE reach 88.60 vs. 94.09 (mean difference -5.490) (Figure 2).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

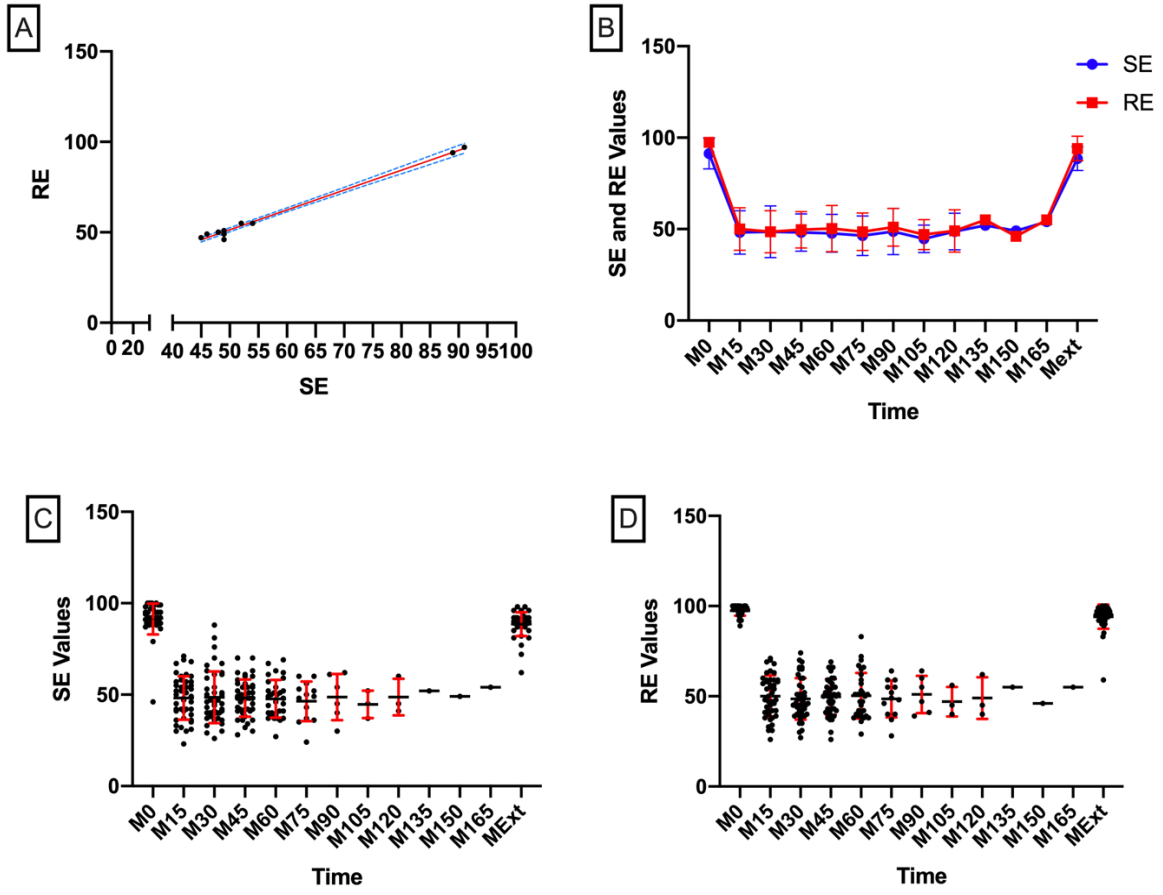

Figure 2. SE and RE expression. A: correlation between SE and RE values, p=0.7620, 95% CI: 0.9812 TO 0.9982, r = 0.9942, R^2 = 0.9884; B: evolution of SE and RE in time; C: expression and allocation of SE in time; D: expression and allocation of RE in time.

An important aspect for general anesthesia in the minimum alveolar concentration of volatile anesthetic agent (MAC). Interestingly enough, in our study the mean MAC value after the first 15 minutes of general anesthesia was 0.8349 for Group A vs. 0.9080 for Group B. Based on the correlations between MAC values and SE, and MAC values and RE in Group A there was no statistical correlation (Figure 3). There was a statistically significant difference for the correlation between MAC values in the two groups (Group A vs. Group B) with p = 0.0008, r = 0.8112, R^2 = 0.6580, and 95% Confidence Interval 0.4705 to 0.9414

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

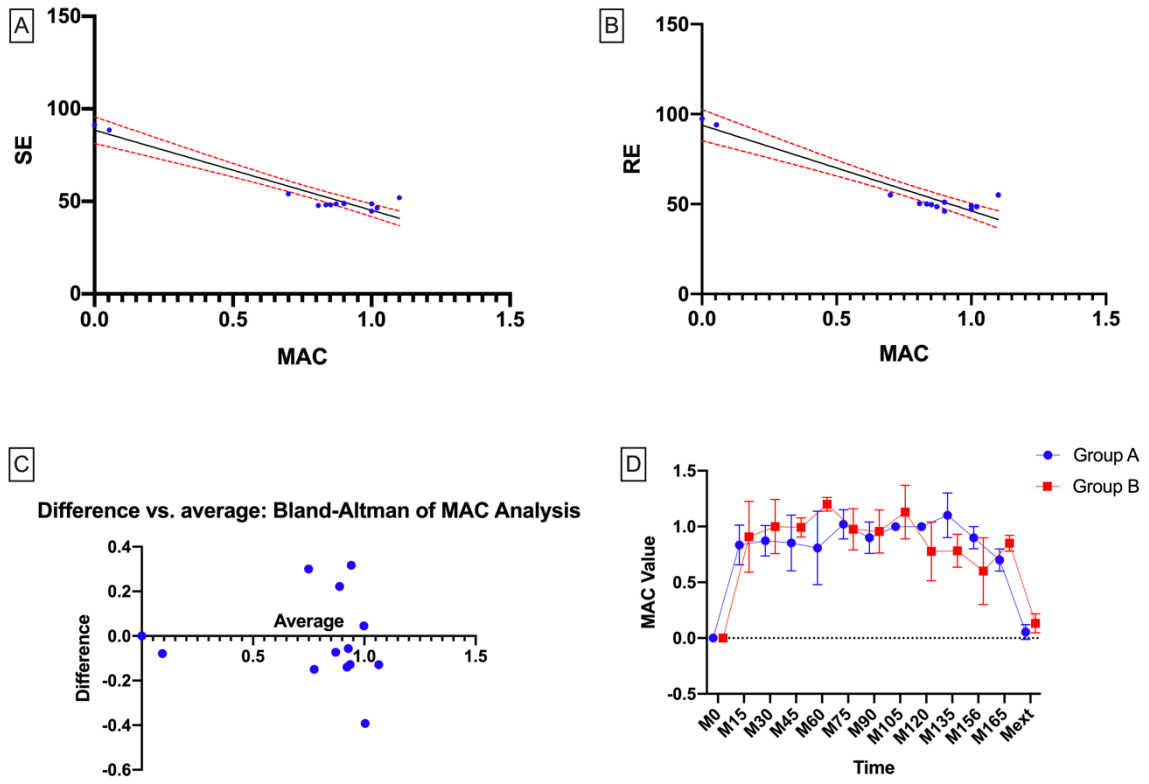

Figure 3. Statistical correlations for MAC and SE/RE. A: correlations for SE and MAC (r = -0.9583, r^2 = 0.9184, 95%CI -0.9878 to - 0.8630); B: correlations for RE and MAC(r = -0.9519, r^2 = 0.9043, 95% CI -0.9855 to -0.8402); C: Bland-Altman analysis of MAC values; D: MAC value over time

The mean OR time for patients in Group A was 73.14 ± 30.14 min vs. 84.60 ± 29.79 for patients in Group B. There were no statistically significant differences between the two groups (p=0.1337, 95% Confidence Interval -3.610 to 26.53, mean difference 11.46 ± 7.548), a very important aspect when analyzing mean Sevoflurane consumption.

Regarding Sevoflurane consumption, Group A showed a mean consumption of 144.1 ± 69.86 mL compared to Group B where the mean was 185.8 ± 60.33. Volatile anesthetic consumption over time has expressed statistically significant differences between the two groups. Group A had a mean consumption of 2.191 ± 1.440 mL/min (lower 95% CI of mean 1.748, upper 95% CI of mean 2.634, variation coefficient 65.73%) vs. Group B 2.446 ± 0.9849 mL/min (lower 95% CI 2.040, upper 95% CI 2.853, variation coefficient 40.26%). The mean difference between the two groups was 0.2553 ± 0.3253, and 95% CI - 0.3942 to 0.9047. Statistically significant differences have been identified between the two groups regarding the consumption of anesthetic gas, with Group A having a lower threshold (p=0.0498) (Figure 4).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

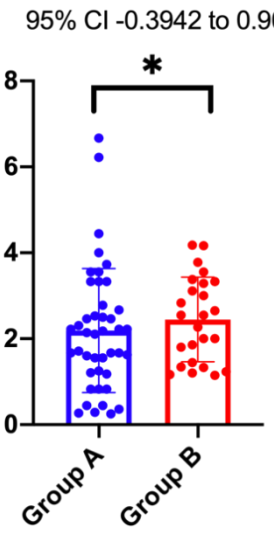

Figure 4. Statistical analysis of Sevoflurane consumption (mL/min) between the two study groups

3.3. Hemodynamic stability during surgery

In the present study hemodynamic stability was assessed based on a number of different parameters. These parameters included: heart rate (HR, bpm), systolic blood pressure (mmHg), and the number of recorded hemodynamic events such as hypotension, hypertension, bradycardia, and tachycardia. In Group A were recorded a number of 1.6/N (N=43) of hemodynamic events, of which 17 (24.4%) – hypertension, 19 (28.4%) hypotension, 12 (17.9%) tachycardia, and 19 (28.4%) bradycardia. In Group B were recorded 2.84/N (N=25) hemodynamic events, of which 21 (29.6%) – hypertension, 14 (19.7%) hypotension, 21 (29.6%) tachycardia, and 15 (21.1%) bradycardia. For a more correct appreciation of the number of adverse hemodynamic events these were reported to the number of patients in each group (Table 2).

Table 2. Hemodynamic changes in study Group A and study Group B

	Group A (N=43)			Group B (N=25)		
	No. Hemodynamic Events	No. Hemodynamic Events / Patient	% of Hemodynamic Events	No. Hemodynamic Events	No. Hemodynamic Events / Patient	% of Hemodynamic Events
No. Hypertensions	17	0,4	25,4	21	0,84	29,6
No. Hypotensions	19	0,5	28,4	14	0,56	19,7
No. Tachycardia	12	0,3	17,9	21	0,84	29,6
No. Bradycardia	19	0,5	28,4	15	0,6	21,1
Total	67	1,6		71	2,84	

For the statistical analysis of the two groups, the results show a significantly lower number of hypotensive events in Group A ($p = 0.011$; 95% CI 0.1851 to 0.7042; min 0 : max 2; 25% Percentile 0, 75% Percentile 1; Range 2). Statistically significant differences were noticed for bradycardia, with a decreased incidence in Group A ($p < 0.0001$; 95% CI 0.3296 to 0.7923; min 0 : max 1; 25% Percentile 1, 75% Percentile 1; Range 1). There were no statistically significant differences for hypertensive events ($p = 0.3547$; 95%CI -0.1349 to 0.3712; min 0 : max 1; 25% Percentile 0, 75% Percentile 1; Range 1) or for tachycardia ($p = 9.2866$; 95%CI -0.1357 to 0.4520; min 0 : max 1; 25% Percentile 0, 75& Percentile 1; Range 1) (Figure 5). The distribution for the number of events in each group shows that in Group A the most of patients experienced no bradycardia, a very low number of patients experienced 1 episode (N=10, 83.33%), and only in isolated cases two bradycardia events were recorded (N=1, 8.37%). On the other hand, in Group B, an increased number of patients experienced at least one episode of bradycardia (N=21, 84%). The hemodynamic changes represented by hypotension follow a similar trend. Most of the patients in Group A, 76.47% presented only one blood pressure drop (hypotension), while only 11.77% presented two hypotensive episodes. In contrast, 86% of patients in Group B presented with one episode of hypotension. Although from the distribution perspective tachycardia and hypertension events were different, these differences were not statistically significant. In the case of tachycardia 84.21% of patients in Group A presented with one episode and 5.26% presented with three episodes. 60% (N=15) of patients in Group B presented with one episode of hypertension. The distribution is similar, being 100% in Group A with one episode and 56% in Group B (Figure 5).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

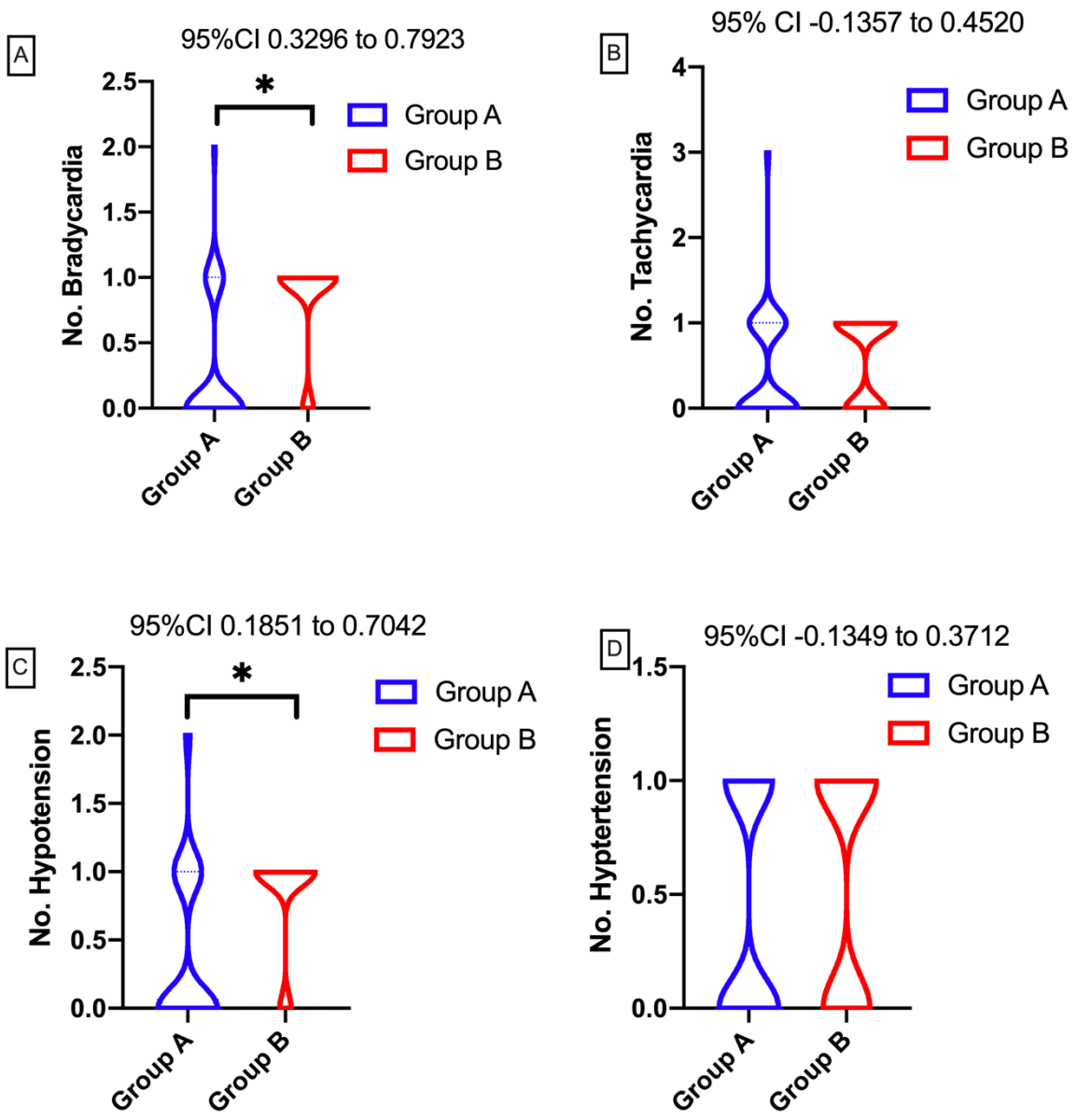

Figure 5. Statistical and graphical analysis of perioperative hemodynamic changes. A: number of bradycardia episodes; B: number of tachycardia episodes; C: number of hypotensive episodes; D: number of hypertensive episodes

The analysis of the dynamics for heart rate (HR, bpm) in the two groups revealed important statistical variations. In Group A there were statistically significant differences recorded for the hemodynamic changes between M0 and M15 ($p < 0.05$), M0 and M30 ($p < 0.05$), M0 and Mext ($p < 0.05$). A similar tendency was recorded for Group B, with significant differences between M0 and M15 ($p < 0.05$), M0 and M30 ($p < 0.05$), M0 and Mext ($p < 0.05$). For systolic blood pressure (SAB, mmHg) differences were statistically significant in Group A between M0 and M15 ($p < 0.05$), M30 ($p < 0.05$), M45 ($p < 0.05$), and M60 ($p < 0.05$). In Group B significant differences were recorded for a longer time span, as follows: M0 and M15 ($p < 0.05$), M30 ($p < 0.05$), M45 ($p < 0.05$), M60 ($p < 0.05$), M75 ($p < 0.05$), M90 ($p < 0.05$), M105 ($p < 0.05$), M120 ($p < 0.05$), M135 ($p < 0.05$), si M150 ($p < 0.05$) (Table 3 and Figure 6).

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

Table 3. Statistical analysis of the dynamics for heart rate and blood pressure

0

HR (bpm)														
		M0	M15	M30	M45	M60	M75	M90	M105	M120	M135	M156	M165	Mext
Group A	MEAN	75,9	75,4	76,1	77,3	79,3	81,8	82,1	82,6	82,7	76,0	74,0	72,0	82,9
	SD	13,9	11,7	12,1	11,3	13,4	12,5	12,2	16,8	10,8	0,0	0,0	0,0	9,8
	p		M15/M0	M30/M0	M45/M0	M60/M0	M75/M0	M90/M0	M105/M0	M120/M0	M135/M0	M150/M0	M165/M0	Mext/M0
			< 0.05	< 0.05	> 0.05	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05	-	-	-	< 0.05
Group B	MEAN	74,9	69,3	67,6	69,9	70,0	75,0	76,4	73,4	75,8	80,5	89,0	89,0	94,6
	SD	14,4	6,3	7,7	9,6	8,9	9,1	8,3	8,8	9,5	10,9	11,1	9,9	18,2
	p		M15/M0	M30/M0	M45/M0	M60/M0	M75/M0	M90/M0	M105/M0	M120/M0	M135/M0	M150/M0	M165/M0	Mext/M0
			< 0.05	< 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	< 0.05	> 0.05	< 0.05
SAP (mmHg)														
Group A	MEAN	136,6	121,4	122,2	122,7	119,3	118,8	130,2	122,7	127,0	0,0	0,0	0,0	136,6
	SD	23,9	24,1	19,8	17,9	14,6	15,1	23,8	4,6	5,2	0,0	0,0	0,0	15,7
	p		M15/M0	M30/M0	M45/M0	M60/M0	M75/M0	M90/M0	M105/M0	M120/M0	M135/M0	M150/M0	M165/M0	Mext/M0
			< 0.05	< 0.05	< 0.05	0< 0.05	< 0.05	> 0.05	> 0.05	> 0.05	-	-	-	> 0.05
Group B	MEAN	134,0	109,9	112,0	118,5	117,7	113,9	112,6	116,6	115,0	114,3	117,8	105,0	129,4
	SD	17,5	16,3	21,0	18,6	19,7	15,5	14,3	11,8	12,5	14,5	19,9	11,3	12,0
	p		M15/M0	M30/M0	M45/M0	M60/M0	M75/M0	M90/M0	M105/M0	M120/M0	M135/M0	M150/M0	M165/M0	Mext/M0
			< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	> 0.05	> 0.05

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 February 2020 doi:10.20944/preprints202002.0130.v1

Peer-reviewed version available at Entropy 2020, 22, 356; doi:10.3390/e22030356

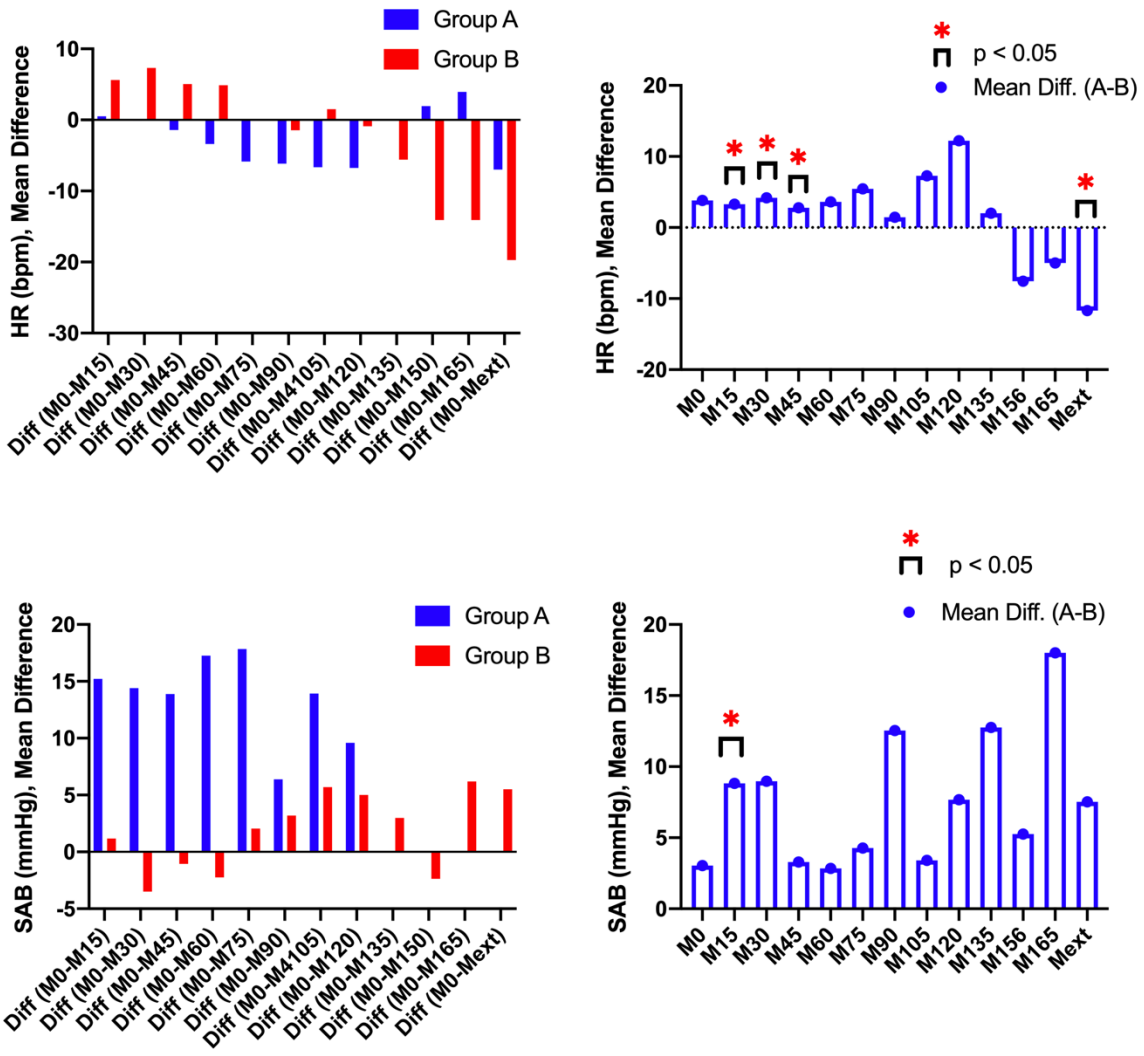

Figure 6. Statistical analysis of mean differences for heart rate (A and B), blood pressure (C and D)

4. Discussion

Common technologies for monitoring degree of hypnosis/depth of anesthesia are represented by BIS, Entropy (SE/RE), and Narcotrend index. From a technical point of view, BIS is based on the analysis of EEG variations. Bispectral analysis is characterized by the sub-variable called ”SynchFastShow” and is mathematically defined as the logarithm of the sum of all bispectral peeks in the 0.5 – 47 Hz interval. Narcotrend index is based on EEG classification at different stages based on the degree of hypnosis. In this manner the stages were classified as ”A = awake” and ”F = very deep level of anesthesia”. The technology is based on the statistical analysis of EEG signals associated with the stages that indirectly account for the depth of anesthesia. For a more user-friendly interface in clinical practice the technology transforms these stages in numerical values in the interval between 0 and 100. The Entropy is a technology that integrates two methods – deciphering of EEG signals and the electromyography (EMG) of face muscles. Therefore, Entropy becomes a mathematical concept used for the interpretation of non-linear dynamic data that gives tow values – state entropy (SE) and response entropy (RE). Technically, SE is characterized by the Shannon Entropy [7], the first discovered and studied parameter. RE shows the regularity of frequency distribution in the 0-47 Hz interval and includes both EEG and EMG activity. In contrast, SE only includes EEG analysis and calculates frequencies in the 0-32 Hz interval [8,9]. In our study the patients in Group A that received multimodal monitoring had a mean value for SE and RE in the reference interval of 40-60. In the

clinical practice there are numerous cases where modulating the depth of anesthesia becomes imperative, especially in the case of elderly patients with many comorbidities. Such a group is represented by patients proposed for cardiac surgery where higher medication doses lead to increased hemodynamic instability. This field has drawn attention to patients needing cardiopulmonary by-pass, as these patients are usually also receiving beta-blockers and other hypotensive medication. In these situations classical monitoring parameters are no longer reliable for monitoring the depth of anesthesia [10]. Another important fact is that recent studies have not shown a strong correlation between BIS and Entropy monitoring in these situations. Lehmann et al., have reported a lack of correlation for BIS and Entropy in their study [11]. A similar study has been carried out by Meybohm et al., showing a very important aspect for cardiac surgery with cardiopulmonary by-pass regarding hypothermia. The group has reported significant correlations between BIS and Entropy under the conditions of normothermia (BIS vs. SE: $r^2 = 0.56$; BIS vs. RE: $r^2 = 0.58$), but lower correlations between the two parameters for hypothermic patients (BIS vs. SE: $r^2 = 0.17$; BIS vs. SE: $r^2 = 0.18$) [12]. Musialowicz et al., have also shown low correlations between BIS and Entropy in patients under cardiopulmonary by-pass[10]. Ma et al., have carried out a study regarding the impact of anesthetic drugs doses in cardiac surgery with cardiopulmonary by-pass. This research group has reported a significant decrease in the propofol and sufentanyl consumption in the case of patients who received Entropy monitoring ($p < 0.05$). Another important factor that M et al. have reported is the positive clinical impact on hemodynamic stability in case of Entropy monitoring, with their control group needing higher vasopressor doses ($p < 0.05$) [13].

From recent clinical practice it is a known fact that surgical procedures that involve a laparotomy imply a longer and more difficult recovery. These patients experience more often a series of adverse phenomena such as lack of energy, prolonged fatigue and a more difficult reintegration in their day-to-day lives. Apart from these the literature has reported other side effects after surgery such as pain, longer periods of analgesic medication, nausea and vomiting, loss of appetite, increased bleeding risk and increased risk for infection. These are some of the reasons why surgical techniques have evolved in the last decade, with laparoscopic surgery becoming routine practice worldwide. Once this new technique was used at a larger scale a series of aspects regarding general anesthesia arose as important parameters for monitoring. One important aspect associated with general anesthesia for laparoscopic surgery is that of perioperative respiratory and ventilatory dysfunctions such as volutrauma, barotrauma and atelectasis. The main cause for these complications is the increased intra-abdominal pressure that pushes the diaphragm and doubles the pressure in the thoracic cavity. By maintaining a higher than normal intra-abdominal pressure the main factor that favor complications are increased pressure, the patient's position and carbon dioxide absorption [14].

In our study one of the main objectives was to monitor the impact of general anesthesia on hemodynamic stability during this type of procedure. The hypothesis was that modulating the anesthetic doses based on the individual needs of each patient might have a positive impact on perioperative hemodynamic stability. In other words our study focused on optimizing the Sevoflurane doses by monitoring the degree of hypnosis/depth of anesthesia based on the Entropy (State Entropy-SE and Response Entropy-RE). The main mechanisms influencing the hemodynamic stability of patients that undergo laparoscopic surgery are the impact on venous return, on myocardial contractility, and the increase in systemic vascular resistance [15]. A high percentage of these patients have a decrease cardiac output with hemodynamic collapse due to increased intra-abdominal pressure that leads to the compression of the inferior vena cava and further decrease of venous return. Furthermore, the increased vascular resistance leads to an increased motor load of the heart with tachycardia, increased blood pressure that can lead to hemodynamic colaps. [16–20]. It is a known fact that one of the pharmacodynamic effects of volatile anesthetics is their impact on the heart function [21–23], but it should be noted that apart from its effects on the hemodynamic status, Sevoflurane also has cardioprotective properties. From a molecular point of view the cardioprotective effects are attained through its action on adenosine triphosphate sensitive channels that can be found in the cardiac myocites. Tanaka et al., have shown that Isoflurane can have a beneficial cardiac

preconditioning effect by modulating mitochondrial potassium channels after the activation of adenosine-triphosphate [24]. The beneficial effects on the clinical prognosis have also been proven for Propofol. Recent studies have shown that total intravenous general anesthesia (TIVA) with Propofol is associated with fewer postoperative side-effects [25–27]. Among these are a decrease in postoperative pain, modulation of the cerebral blood flow, a decrease in intracranial pressure, and a lower incidence of postoperative nausea and vomiting. The study carried out by Kawano et al., on the implications of Propofol and Sevoflurane on the postoperative side-effects concludes that by using this drug combination the incidence of specific side-effects is significantly lower [28]. In our study we have shown that by optimizing the doses of inhalational anesthetic guided by Entropy we obtained better hemodynamic stability. In the patients included in the study group (Group A) we have noticed a statistically significant decrease in the incidence of hypotensive episodes ($p<0.05$), as well as in the incidence of bradycardia ($p<0.05$). No implications have been noticed for tachycardia or hypertensive episodes ($p>0.05$).

A series of recent studies and recommendations have proven the need for implementing multimodal monitoring protocols in general anesthesia for laparoscopic surgery. Most of them refer to hemodynamic and respiratory monitoring. In the recent years there have been extensive debates on introducing as routine the monitoring protocols for parameters capable of determining the depth of anesthesia, the nociception – anti-nociception balance, and the neuromuscular transmission [29–31]. In regard to hemodynamic monitoring the balance favors the invasive monitoring of arterial blood pressure. In the case of patients with associated cardiovascular comorbidities, monitoring techniques are more complex, bringing vital information on the filling pressure of the heart, on the preload and systemic pressure distribution. Regarding mechanical ventilation, in the case of patients undergoing laparoscopic surgery, pressure based ventilation is preferred. Moreover, PEEP titration based on the clinical context reduces the specific side-effects of alveolar collapse [32]. More attention should be given to the cardiovascular stability of these patients and to a continuous adaptation of the PEEP value based on their hemodynamic profile [33–35].

Numerous studies have shown a series of correlations between BIS and the anesthetic doses, incidence of side-effects or recovery time, but only a few have shown strong statistical correlation between the plasmatic concentration of anesthetic drugs and the BIS signal expression [8,36]. This fact comes only to confirm the need for an individualized approach towards general anesthesia based on the particular needs of each patient. Shah et al., have carried out a study on the impact that entropy monitoring can have on the hemodynamic status and have reported a positive influence on hemodynamic stability, as well as a reduction in anesthetic doses [37]. A similar study carried out by Riad et al., reported a reduction in Propofol doses with 37.1% in the Entropy monitoring group compared to the control ($p<0.05$) [38]. Tewari et al., have studied the recovery time and the anesthetic drug doses in patients that underwent transvaginal oocyte retrieval under general anesthesia. The study group have proven that entropy monitoring led to a decreased Propofol consumption with 6.7% ($p=0.01$). They have also reported needing lower opioid (Fentanyl) doses ($p=0.007$). An important aspect has been noted in the recovery room where in the case of the group with entropy monitoring only 10% of the patients needed supplemental post-operative analgesia, compared to the control group where 28.3% of patients needed supplementation ($p=0.01$) [39]. Wu et al., have also reported a statistically significant decrease ($p<=0.05$) for Sevoflurane consumption in the entropy group (27.79 ± 7.4 mL vs. 31.42 ± 6.9 mL). Furthermore, they have proven the positive impact on hemodynamic stability compared to the control group ($p = 0.043$) [40]. In our study we have identified a similar trend as Group A had a significantly lower Sevoflurane consumption compared to the control group ($p = 0.0498$). Another study on the impact of entropy on anesthetic drug doses was carried out by Vakkuri et al., reporting significant differences between their study groups, with a positive impact on recovery time in the case of patients that benefited from entropy monitoring [41]. El Hor et al., carried out a similar study on patients undergoing laparoscopic rectosigmoidectomy. They have reported decreased Sevoflurane consumption in the group where general anesthesia has been optimized by using the entropy (5.2 ± 1.4 mL/h vs. 3.8 ± 1.5 mL/h, $p = 0.0012$). For the same group

they have reported improved hemodynamic stability, with a decrease in the hypotension incidence ($p = 0.03$) [42].

Postoperative recovery is another very important aspect, both from the functional and the cognitive point of view [43]. It is a well-known fact the surgical stress and general anesthesia can impact cognitive and neurological recovery. Zhang et al., have carried out a study on th impact of Sevoflurane and Propofol in on the neuro-cognitive recovery. They have concluded that intravenous anesthesia with Propofol has less side-effects that inhalational anesthesia with Sevoflurane [44]. This is another essential argument for introducing hypnosis monitoring based on EEG analysis. Kadoi et al. have proven in their study a minimization of neurological impact in the case of intravenous anesthesia with Propofol in the elderly [45]. A similar study carried out by Radtke et al., on the implications of depth of anesthesia monitoring on the post-operative recovery. They have observed a delirium incidence of only 16.7% in the group where depth of anesthesia was monitored compared with 21.5% in the control group ($p = 0.036$). They have also shown the lack of cognitive imbalance later on, but with no significant differences at 7 days ($p = 0.062$), and at 90 days ($p = 0.372$) [46]. Postoperative complication rate has been shown to vary between 20% and 42% [47]; they have an impact both on the clinical outcome of patients, as well as on the OR management and patient outflow [48]. This is due to longer times of stay in the recovery room and longer hospital length of stay [49–52]. Another important aspect directly connected to the postoperative complications is the economical aspect of the medical system, with increased costs in these situations. The main causes for secondary complications are hemodynamic instability with a direct effect on dopaminergic, muscarinic and serotoninergic receptors. The central and peripheral opioid receptors are also affected by both over- or under-dosing of anesthetic drugs [53–57].

One limitation of these monitoring techniques is the lack of evidence in pediatric patients. Both entropy and BUS present low statistical correlations in the pediatric population under 1 year of age. Davidson et al., have studied the performance of BIS and Entropy in different pediatric groups. They have designed different study groups for certain age intervals 0-1 years, 1-2 years, 2-4 years, and 4-12 years. Following this study they concluded that for children under the age of 1 there are big differences between the measurements both for Entropy and for BIS. They did not report significant differences between the two technologies [58]. Another limitation of both the technologies is given by the concomitent administration of ketamine [59]. Once ketamine is administerd the value of both parameters are increased and the correlations are no longer valid. Hans et al., have studied the effects induced by ketamine on the depth of anesthesia monitoring techniques and have reported a significant change in the expression of BIS/SE/RE [60].

One very important aspect is represented by the environmental impact of volatile anesthetics. From a chemical point of view, volatile anesthetic gases are organic halogenated compounds that negatively impact the ozone layer. Moreover, they persist in the atmosphere for longer periods of time, contributing to global warming. Brown et al., in a study on the impact of anesthetic gases – halotane, desflurane, and enflurane on the ozone layer concluded that their remanence time is 2.5 to 21.4 years [61]. Apparently the volumes used seem small but worldwide annually pharmaceutical companies deliver millions of liters of volatile anesthetics. A recent study estimated that a medium sized hospital in the US uses around 1000 L of volatile anesthetic yearly[62].

The limitations of our study are the lack of monitoring for the nociception-anti-nociception balance and that no correlations have been made between this parameter and the consumption of Fentanyl. Last but not least the study did not focus on the post-operative recovery time and no data have been collected on the neurocognitive recovery at 24 and 48 hours.

5. Conclusions

In conclusion we can say that multimodal monitoring that includes both classical parameters and monitoring of the depth of anesthesia through Entropy improves perioperative hemodynamic stability. Our study has shown a decreased incidence for both hypotension and bradycardia episodes in the group that benefited from multimodal monitoring with personalized anesthetic dosage based on the Entropy value. Furthermore, we have recorded a decrease in Sevoflurane consumption in the group where general anesthesia was optimized with the help of Entropy.

We can conclude that by adapting the general anesthetic technique based on the individual needs of each patient, clinicians can achieve and individualized anesthesia with a significant positive impact on perioperative hemodynamic stability and on the consumption of volatile anesthetics. Finally we can underline the increase in patient safety and the improved therapeutic management by adapting current practice towards a personalized medicine tailored for the individual needs of each patient.

Author Contributions: Conceptualization, A.R.D., A.F.R., M.P., A.M., and D.S.; methodology, A.R.D., O.H.B., M.P., L.L., A.M; software, C.M.D., D.T., and L.I.T.; validation, C.B., M.A.S., and D.S.; formal analysis, A.R.D., S.E.P., O.H.B., M.P., C.M.D., R.R.V., D.T., C.M.G., L.I.T., C.B., S.R., and D.S..; investigation, A.F.R., S.E.P., R.R.V., C.B., L.L., B.B., A.M., M.A.S., S.R., M.M.V., and P.L.; resources, C.M.D., M.A.S., and S.R.; data curation, A.D.R., S.E.P., O.H.B., D.T., C.M.G., L.I.T., C.B., B.B., M.A.S., S.R., M.M.V., L.M.B., and P.L; writing—original draft preparation, A.R.D., S.E.P., B.B., M.A.S., S.R., and M.M.V.; writing—review and editing, D.S.; visualization, A.F.R., R.R.V., L.I.T., B.B., and P.L; supervision, D.S.; project administration, X.X.; funding acquisition, S.E.P., O.H.B., L.L., L.M.B., and P.L. All authors have read and agreed to the published version of the manuscript.

Funding: Romanian Society of Anaesthesia and Intensive Care, Department for Clinical Research and Medical Education, Timisoara, Romania

Acknowledgments: This article was published with the support from the Association for Anaesthesia and Intensive Care "Aurel Mogoseanu", Timisoara, Romania and ”Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kanakala, V.; Borowski, D.W.; Pellen, M.G.C.; Dronamraju, S.S.; Woodcock, S.A.A.; Seymour, K.; Attwood, S.E.A.; Horgan, L.F. Risk factors in laparoscopic cholecystectomy: A multivariate analysis. *Int. J. Surg.* **2011**, *9*, 318–323.

2. Ellakany, M. Comparative study between general and thoracic spinal anesthesia for laparoscopic cholecystectomy. *Egypt. J. Anaesth.* **2013**, *29*, 375–381.

3. Wycherley, A.S.; Bembridge, J.L. Monitoring techniques; neuromuscular blockade and depth of anaesthesia. *Anaesth. Intensive Care Med.* **2017**, *18*, 324–327.

4. Ozdogan, H.K.; Cetinkunar, S.; Karateke, F.; Cetinalp, S.; Celik, M.; Ozyazici, S. The effects of sevoflurane and desflurane on the hemodynamics and respiratory functions in laparoscopic sleeve gastrectomy. *J. Clin. Anesth.* **2016**, *35*, 441–445.

5. Rogobete, A.F.; Bedreag, O.H.; Sandesc, D. Entropy-Guided Depth of Anesthesia in Critically Ill Polytrauma Patients. *J. Interdiscip. Med.* **2017**, *2*, 7–8.

6. Cotae, A.; Grinţescu, I.M. Entropy — The Need of an Ally for Depth of Anesthesia Monitoring in Emergency Surgery. **2019**, 13–15.

7. Shalbaf, R.; Behnam, H.; Sleigh, J.W.; Steyn-Ross, A.; Voss, L.J. Monitoring the depth of anesthesia using entropy features and an artificial neural network. *J. Neurosci. Methods* **2013**, *218*, 17–24.

8. Bruhn, J.; Myles, P.S.; Sneyd, R.; Struys, M.M.R.F. Depth of anaesthesia monitoring: What's available, what's validated and what's next? *Br. J. Anaesth.* **2006**, *97*, 85–94.

9. Ortolani, O.; Conti, A.; Di Filippo, A.; Adembri, C.; Moraldi, E.; Evangelisti, A.; Maggini, M.; Roberts, S.J. EEG signal processing in anaesthesia. Use of a neural network technique for monitoring depth of anaesthesia. *Br. J. Anaesth.* **2002**, *88*, 644–648.

10. Musialowicz, T.; Lahtinen, P.; Pitkänen, O.; Kurola, J.; Parviainen, I. Comparison of Spectral Entropy and BIS VISTA™ monitor during general anesthesia for cardiac surgery. *J. Clin. Monit. Comput.* **2011**, *25*, 95–103.

11. Lehmann, A.; Schmidt, M.; Zeitler, C.; Kiessling, A.-H.; Isgro, F.; Boldt, J. Bispectral index and electroencephalographic entropy in patients undergoing aortocoronary bypass grafting. *Eur. J. Anaesthesiol.* **2007**, *24*, 751–760.

12. MEYBOHM, P.; GRUENEWALD, M.; HÖCKER, J.; RENNER, J.; GRAESNER, J.-T.; ILIES, C.; SCHOLZ, J.; BEIN, B. Correlation and agreement between the bispectral index vs. state entropy during hypothermic cardio-pulmonary bypass. *Acta Anaesthesiol. Scand.* **2010**, *54*, 169–175.

13. Ma, J.; Wang, X.; Xie, Y.; Yu, J.; He, Q.; Li, Z.; Du, J.; Jiang, X. Spectral entropy monitoring reduces anesthetic dosage for patients undergoing off-pump coronary artery bypass graft surgery. *J. Cardiothorac. Vasc. Anesth.* **2012**, *26*, 818–821.

14. Vargas, M.; Brunetti, I.; Pelosi, P. Protective mechanical ventilation during general anaesthesia. *Trends Anaesth. Crit. Care* **2013**, *3*, 77–81.

15. Kim, D.; Ahn, J.H.; Jung, H.; Choi, K.Y.; Jeong, J.S. Effects of neuromuscular blockade reversal on bispectral index and frontal electromyogram during steady-state desflurane anesthesia: a randomized trial. *Sci. Rep.* **2019**, *9*, 1–7.

16. Rosa, R.C. De; Romanelli, A.; Calabria, M.; Abbate, R.; Montesano, R.; Corcione, A. Continuous Noninvasive Haemoglobin Monitoring in Vascular Surgery within the Goal-Directed Therapy Protocol Abstract : **2019**, *1*, 1–15.

17. Cotrau, P.; Hodosan, V.; Vladu, A.; Timar, C.; Daina, L.; Pantis, C.; Negrau, M.; Daina, C.; Vernic, C. Occupational Stress and Burnout Syndrome among ICU Nurses . A Prospective Observational Study. *1*, 1–10.

18. Moise, A.; Balescu-arion, C. Central European Annals of Clinical Research The Vitamin D and the Immune System . When ? Why ? How ? **2020**, *2*, 1–9.

19. Georgescu, D.; Reisz, D.; Petre, I.; Ionita, I. Ischemic Stroke Secondary to Cerebral Venous Thrombosis : A Case Report. **2019**, 1–7.

20. Colombo, R.; Raimondi, F.; Rech, R.; Castelli, A.; Fossali, T.; Marchi, A.; Borghi, B.; Corona, A.; Guzzetti, S. Surgical Pleth Index guided analgesia blunts the intraoperative sympathetic response to laparoscopic cholecystectomy. *Minerva Anestesiol.* **2015**, *81*, 837–845.

21. Xie, P.; Li, Z.; Tian, Z. The optimal combination of mechanical ventilator parameters under general anesthesia in obese patients undergoing laparoscopic surgery. *J. Clin. Anesth.* **2016**, *34*, 290–294.

22. Feldman, L.S.; Kaneva, P.; Demyttenaere, S.; Carli, F.; Fried, G.M.; Mayo, N.E. Validation of a physical activity questionnaire (CHAMPS) as an indicator of postoperative recovery after laparoscopic cholecystectomy. *Surgery* **2009**, *146*, 31–39.

23. Papurica, M.; Sandesc, D.; Rogobete, A.F.; Nartita, R.; Vernic, C.; Popovici, S.E.; Bedreag, O.H. Cardioprotective Effects Induced by Preconditioning with Halogenated Anesthetics. **2016**, *1*, 23–31.

24. Tanaka, K.; Weihrauch, D.; Ludwig, L.M.; Kersten, J.R.; Pagel, P.S.; Warltier, D.C. Mitochondrial adenosine triphosphate-regulated potassium channel opening acts as a trigger for isoflurane-induced preconditioning by generating reactive oxygen species. *Anesthesiology* **2003**, *98*, 935–943.

25. Metry, A.A.; Hussain, N.S.; Nakhla, G.M.; Ragaei, M.Z.; Wahba, R.M. The effect of continuous propofol versus dexmedetomidine infusion on regional cerebral tissue oxygen saturation during cardiopulmonary bypass. **2019**, *26*, 17–23.

26. Riazanova, O. V; Alexandrovich, Y.S.; Guseva, Y. V; Ioscovich, A.M. A randomized comparison of low dose ropivacaine programmed intermittent epidural bolus with continuous epidural infusion for labour analgesia. **2019**, *26*, 25–30.

27. Balan, S.A.; Bubenek-turconi, Ş.I.; Droc, G.; Marinescu, E.; Nita, E.; Popa, C.; Popescu-spineni, D.; Tomescu, D. Burnout syndrome in the Anaesthesia and Intensive Care Unit. **2019**, *26*, 31–36.

28. Kawano, M.; Tanaka, K.; Itonaga, I.; Iwasaki, T.; Tsumura, H. C-Myc represses tumor-suppressive microRNAs, let-7α, miR-16 and miR-29b, and induces cyclin D2-mediated cell proliferation in Ewing's sarcoma cell line. *PLoS One* **2015**, *10*, 1–17.

29. Maestroni, U.; Sortini, D.; Devito, C.; Morad, F.P.; Brunaldi, K.; Anania, G.; Pavanelli, L.; Pasqualucci, A.; Donini, A. A new method of preemptive analgesia in laparoscopic cholecystectomy. **2002**, 1336–1340.

30. Bedreag, O.H.; Rogobete, A.F.; Sandesc, D.; Cradigati, C.A.; Sarandan, M.; Popovici, S.E.; Dumache, R.; Horhat, F.G.; Vernic, C.; Sima, L. V; et al. Modulation of the Redox Expression and Inflammation Response in the Crtically Ill Polytrauma Patient with Thoracic Injury . Statistical Correlations between Antioxidant Therapy and Clinical Aspects . A Retrospective Single Center Study. **2016**, 1–13.

31. David, V.L.; Ercisli, F.; Florin, A.; Boia, E.S.; Nitu, R. Early Prediction of Sepsis Incidence in Critically Ill Patients Using Specific Genetic Polymorphisms. **2017**, *55*, 193–203.

32. Choi, S.; Yang, S.Y.; Choi, G.J.; Kim, B.G.; Kang, H. Comparison of pressure- and volume-controlled ventilation during laparoscopic colectomy in patients with colorectal cancer. *Sci. Rep.* **2019**, 1–10.

33. Hayden, P.; Cowman, S. Anaesthesia for laparoscopic surgery. *Contin. Educ. Anaesthesia, Crit. Care Pain* **2011**, *11*, 177–180.

34. Berger, M.M.; Que, Y.A. A protocol guided by transpulmonary thermodilution and lactate levels for resuscitation of patients with severe burns. *Crit. Care* **2013**, *17*, 195.

35. Küntscher, M. V.; Germann, G.; Hartmann, B. Correlations between cardiac output, stroke volume, central venous pressure, intra-abdominal pressure and total circulating blood volume in resuscitation of major burns. *Resuscitation* **2006**, *70*, 37–43.

36. Li, T.N.; Li, Y. Depth of anaesthesia monitors and the latest algorithms. *Asian Pac. J. Trop. Med.* **2014**, *7*, 429–437.

37. Shah, S.; Chowdhury, I.; Bhargava, A.; Sabbharwal, B. Comparison of hemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels. *J. Anaesthesiol. Clin. Pharmacol.* **2015**, *31*, 180.

38. Riad, W.; Schreiber, M.; Saeed, a B. Monitoring with EEG entropy decreases propofol requirement and maintains cardiovascular stability during induction of anaesthesia in elderly patients. *Eur. J. Anaesthesiol.* **2007**, *24*, 684–8.

39. Tewari, S.; Bhadoria, P.; Wadhawan, S.; Prasad, S.; Kohli, A. Entropy vs standard clinical monitoring using total intravenous anesthesia during transvaginal oocyte retrieval in patients for in vitro fertilization. *J. Clin. Anesth.* **2016**, *34*, 105–112.

40. Wu, S.C.; Wang, P.C.; Liao, W.T.; Shih, T.H.; Chang, K.A.; Lin, K.C.; Chou, A.K. Use of spectral entropy monitoring in reducing the quantity of sevoflurane as sole inhalational anesthetic and in decreasing the need for antihypertensive drugs in total knee replacement surgery. *Acta Anaesthesiol. Taiwanica* **2008**, *46*, 106–111.

41. Vakkuri, A.; Ph, D.; Yli-hankala, A.; Ph, D.; Sandin, R.; Ph, D.; Mustola, S.; Ph, D. Spectral Entropy Monitoring Is Associated with Reduced Propofol Use and Faster Emergence in Propofol – Nitrous Oxide – Alfentanil Anesthesia. **2005**, *0*, 274–279.

42. El Hor, T.; Van Der Linden, P.; De Hert, S.; Melot, C.; Bidgoli, J. Impact of entropy monitoring on volatile anesthetic uptake. *Anesthesiology* **2013**, *118*, 868–873.

43. Voss, L.; Sleigh, J. Monitoring consciousness: the current status of EEG-based depth of anaesthesia monitors. *Best Pract. Res. Clin. Anaesthesiol.* **2007**, *21*, 313–325.

44. Zhang, Y.; Shan, G.J.; Zhang, Y.X.; Cao, S.J.; Zhu, S.N.; Li, H.J.; Ma, D.; Wang, D.X. Propofol compared with sevoflurane general anaesthesia is associated with decreased delayed neurocognitive recovery in older adults. *Br. J. Anaesth.* **2018**, *121*, 595–604.

45. Kadoi, Y.; Kawauchi, C.; Saito, S.; Takahashi, K. The comparative effects of equipotent Bispectral Index dosages of propofol and sevoflurane on cerebrovascular carbon dioxide reactivity in elderly patients. *J. Clin. Anesth.* **2009**, *21*, 173–177.

46. Radtke, F.M.; Franck, M.; Lendner, J.; Krüger, S.; Wernecke, K.D.; Spies, C.D. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br. J. Anaesth.* **2013**, *110*, 98–105.

47. Llanes-garza, H.A.; López-cabrera, N.G.; Vega, R.C.; Palacios-rios, D. Efficacy of antiemetic therapy in patients undergoing laparoscopic cholecystectomy. *Med. Univ.* **2015**, *17*, 143–146.

48. Bedreag, O.H.; Papurica, M.; Rogobete, A.F.; Sarandan, M.; Cradigati, C.A.; Vernic, C.; Dumbuleu, C.M.; Nartita, R.; Sandesc, D. New perspectives of volemic resuscitation in polytrauma patients: a review. *Burn. Trauma* **2016**, *4*, 5.

49. Bedreag, O.H.; Rogobete, A.F.; Sarandan, M.; Cradigati, A.C.; Papurica, M.; Dumbuleu, M.C.; Chira, A.M.; Rosu, O.M.; Sandesc, D. Oxidative stress in severe pulmonary trauma in critical ill patients. Antioxidant therapy in patients with multiple trauma--a review. *Anaesthesiol. Intensive Ther.* **2015**, *47*, 351–359.

50. Papurica, M.; Rogobete, A.F.; Sandesc, D.; Cradigati, C.A.; Sarandan, M.; Crisan, D.C.; Horhat, F.G.; Boruga, O.; Dumache, R.; Nilima, K.R.; et al. The Expression of Nuclear Transcription Factor Kappa B (NF-kappaB) in the Case of Critically Ill Polytrauma Patients with Sepsis and Its Interactions with microRNAs. *Biochem. Genet.* **2016**, *54*, 337–347.

51. Horhat, F.G.; Gundogdu, F.; David, L. V.; Boia, E.S.; Pirtea, L.; Horhat, R.; Cucui-Cozma, A.; Ciuca, I.; Diaconu, M.; Nitu, R.; et al. Early Evaluation and Monitoring of Critical Patients with Acute Respiratory Distress Syndrome (ARDS) Using Specific Genetic Polymorphisms. *Biochem. Genet.* **2017**, *55*, 204–211.

52. Dinu, A.R.; Rogobete, A.F.; Bratu, T.; Popovici, S.E.; Bedreag, O.H.; Papurica, M.; Bratu, L.M.; Sandesc, D. Cannabis Sativa Revisited — Crosstalk between Stress , and Endocannabinoid Response System in. 1–23.

53. Longo, M.A.; Cavalheiro, B.T.; Filho, G.R.D.O. Laparoscopic cholecystectomy under neuraxial anesthesia compared with general anesthesia : Systematic review and meta-analyses. *J. Clin. Anesth.* **2017**, *41*, 48–54.

54. Fleming, N.; Cockerham, R. General anaesthesia for operative obstetrics. *Anaesth. Intensive Care Med.* **2019**, *20*, 495–499.

55. Cumpanas, A.A.; Bardan, R.; Ferician, O.C.; Latcu, S.C.; Duta, C. Does previous open surgical experience have any influence on robotic surgery simulation exercises ? **2017**, 366–371.

56. Vãrcuæ, F.; Duåã, C.; Dobrescu, A.; Lazãr, F.; Papurica, M.; Tarta, C. Laparoscopic Repair of Inguinal Hernia TEP versus TAPP. **2016**, 308–312.

57. Papurica, M.; Rogobete, A.F.; Sandesc, D.; Dumache, R.; Nartita, R.; Sarandan, M.; Cradigati, A.C.; Luca, L.; Vernic, C.; Bedreag, O.H. Redox Changes Induced by General Anesthesia in Critically Ill Patients with Multiple Traumas. *Mol. Biol. Int.* **2015**, *2015*, 238586.

58. Davidson, A.J.; Huang, G.H.; Rebmann, C.S.; Ellery, C. Performance of entropy and Bispectral Index as measures of anaesthesia effect in children of different ages. *Br. J. Anaesth.* **2005**, *95*, 674–679.

59. Zgaia, A.O.; Irimie, A.; Sandesc, D.; Vlad, C.; Lisencu, C.; Rogobete, A.; Achimas-Cadariu, P. The role of Ketamine in the treatment of chronic cancer pain. *Clujul Med.* **2015**, *88*.

60. Hans, P.; Dewandre, P.; Brichant, J.F.; Bonhomme, V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. **2005**, *94*, 336–340.

61. Brown, A.C.; Canosa-Mas, C.E.; Parr, A.D.; Pierce, J.M.T.; Wayne, R.P. Tropospheric lifetimes of halogenated anaesthetics. *Nature* **1989**, *341*, 635–637.

62. Yasny, J.S.; White, J. Environmental implications of anesthetic gases. *Anesth. Prog.* **2012**, *59*, 154–158.