

Neurally Adjusted Ventilatory Assistance and Synchronized Intermittent Mandatory Ventilation in Children Assessed by Electrical Impedance Segmentography: A Prospective Randomized Case-Control Crossover Trial

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Research

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Abstract

Background: Assessing relative differences of integrated impedance as a surrogate of volume changes between neurally adjusted ventilatory assist (NAVA) and synchronized intermittent mandatory ventilation (SIMV) by using electric impedance segmentography in children.

Methods: Performed as a prospective randomized case-control crossover trial in a pediatric intensive care unit of a tertiary center including eight mechanically-ventilated children, four sequences of two different ventilation modes were consecutively applied. The children were randomized in two groups; one that was started on neurally adjusted ventilatory assist and the other on synchronized intermittent mandatory ventilation. During ventilation, electric impedance segmentography measurements were recorded.

Results: The relative difference of vertical impedance between both ventilatory modes was measured (median 0.52, IQR 0-0.87). These differences in left apical lung segments were present during the first (median 0.58, IQR 0-0.89, $p=0.04$) and second crossover (median 0.50, IQR 0-0.88, $p=0.05$) as well as across total impedance (0.52 IQR 0-0.87; $p=0.002$). During neurally adjusted ventilatory assist children showed a shift of impedance towards caudal lung segments, compared to synchronized intermittent mandatory ventilation.

Conclusion: Electrical impedance segmentography enables dynamic monitoring of transthoracic impedance. Segmental measurements, however, were of low reproducibility due to various limiting factors in its application. For further evaluation, larger prospective clinical trials are necessary.

Introduction

Keeping patients spontaneously breathing (except in cases of severe lung disease) was emphasized during the 2017 Pediatric Mechanical Ventilation Consensus Conference in 2017.(1) Pediatric intensive care unit (PICU) patients, however, mainly require mechanical ventilation due to various diagnoses. Synchronized intermittent mandatory ventilation (SIMV) has shown to be a lung-protective strategy in pediatric intensive care.(2) However, during SIMV, asynchrony has been described as pronounced (3) when compared to neurally adjusted ventilatory assist (NAVA).(4) Because of patient-ventilator-asynchrony, the need for increased doses of sedation in ventilated children has been documented.(4) Furthermore, several studies have documented cases when mechanical ventilation caused diaphragmatic atrophy in pediatric patients.(5–7) NAVA, on the other hand, is triggered by the patients' diaphragmatic neural breathing effort (8) by placement of a special esophageal tube. Electrical activity of the diaphragm (E_{adi}) is monitored and used as a trigger for inducing assisted ventilatory support. NAVA is varying in its support accordingly to the signals, as well as controlling the level of pressure during ventilation. This triggering mechanism enables improved patient-ventilator-synchrony(8, 9) and therefore reduces the need for sedation.(4, 10) According to a recent study, children that underwent cardiac surgery had lower positive inspiratory pressure (PIP) levels on NAVA compared to children on SIMV.(4) NAVA has also been associated with a greater extubation success.(11) To assess different forms of ventilation strategies in

children, various radiation-free imaging modalities such as lung ultrasound(12), electrical impedance tomography (EIT)(13) and segmentography (EIS)(14) have been employed. Measurements of impedance therefore enables clinicians to draw conclusions about global and regional ventilation of the lung in spontaneously breathing, as well as in mechanically-ventilated children.(13, 15) Since segmentography of lung impedance is a somewhat new imaging method in pediatrics, the aim of this study was to evaluate the efficacy of this bedside tool and evaluate the reproducibility of measurements recorded during pressure-controlled and breath-supported mandatory ventilation (SIMV (PC) PS) compared to NAVA in critically-ill children.

Methods

Setting

After approval of the ethics committee of the Medical University of Vienna (MUV, EK No 1668/2018) we performed a prospective single-center randomized crossover trial at the Department of Pediatrics and Adolescent Medicine. The trial was conducted from April 2019 until June 2020 at the neonatal (NICU) and pediatric intensive care unit (PICU).

Patients

Included were children up to 12 months of age, mechanically ventilated and hemodynamically stable in the preceding 24 hours of the intervention. Children with phrenic palsy or on muscle relaxants were omitted from the inclusion criteria. Ventilation was performed with a Servo-u ventilator (Marquet Critical Care, Solna, Sweden). All children included in this study already had suitable nasogastric tubes for performing NAVA, according to clinical indications made by independent physicians of the ICU. The patients were randomly assigned in two groups (SIMV and NAVA groups). This crossover study was performed in accordance to previously-described pediatric studies.(16, 17) Each ventilation sequence was five minutes in length. In order to avoid false positive and false negative effects of subsequent sequences due to rapid changes between NAVA and SIMV, washout phases with SIMV (PC) PS were carried out in five-minute intervals after each ventilation mode change, following the protocol of Lee et al.(17) The SIMV group, starting in SIMV (PC) PS mode, were switched to NAVA after a washout period. This mode change was performed three times. The NAVA group did so inversely; starting in NAVA and ending in SIMV (PC) PS mode (Fig. 1). Each ventilation mode and washout phase was five minutes in duration. Since the diaphragmatic activity decreased during SIMV (PC) PS sequences, the planned five minutes for NAVA started after reappearing E_{adi} signals. Ventilator settings were adjusted to maintain respiratory minute volume for SIMV (PC) PS and NAVA. EIS measurements were only taken into account during the ventilation sequences; not during the washout phases.

Electrical impedance segmentography

By measuring resistivity of different tissues to a small alternating current impedance results. For electrical segmentographic impedance measurements, the Angelie[→] EIS system (EMS Handelsgesellschaft m.b.H.,

Korneuburg, Austria) was applied. This system displays the division of electrical impedance of four lung segments (Fig. 2). Ten electrodes were applied: five ventrally and five on the dorsal thoracic area. For the alternating current (AC) measurements of impedance, two of the 10 electrodes were placed central to the thorax. These two electrodes formed the center for the remaining eight electrodes: four on each side of the thorax in the middle of each thoracic quadrant. The Angelie[®] processing unit automatically modulates the electrical current in accordance with electric resistance, which is kept between 10 to 500 μ A. The AC works with a frequency of approximately five kHz. Changes of impedance are measured by the other eight electrodes with a sampling frequency of approximately 50 kHz. The processing unit is connected to each electrode. By spectral analysis and with high- and low-pass filters, data is processed onto an image, depicting a trend in impedance values. Ten single electrodes with matching cords were placed as described on thoracotomized children. The single electrodes had to be plugged in individually, in contrast to the butterfly electrodes, which only have one combined patch cable. For non-thoracotomized children, regular placement of the electrodes along the medioclavicular line was possible. For this purpose, butterfly electrodes (Spes Media Srl, Genoa, Italy) combining four external and one central electrode were used.

Statistics

All statistical analyses were performed with IBM SPSS Statistics Version 27 (IBM Corp., Armonk, NY) and RStudio Version 1.3.1093. (RStudio Team (2020), RStudio Integrated Development for R. RStudio, PBC, Boston, MA). For sample-size calculation, a bilateral p-value of 0.05 and power of 0.8 were provided. After performing a pilot study with three children, we estimated a standard deviation of differences between the individual total impedance values of SIMV and NAVA at 20%. Due to the short amount of time required (approximately 45 minutes for each child) and the safe methodology, no more than one child was expected to drop out. Descriptive statistics were presented, depending on the nature of values, as mean \pm standard deviation (SD), median and percentages. Segmental data exported from the EIS device was processed into variables of total thoracic, horizontal and segmental impedance. Horizontal impedance was obtained by calculating the percentage of the left in relation to the total impedance. Similarly, the percentage of the upper impedance was used as a marker for vertical impedance. The median value of total and segmental electrical impedance for each child and each five-minute ventilation sequence was calculated. A median relative difference of impedance change was generated for each child and for every change of ventilation mode, including the first change from NAVA₁ to SIMV₁ until the last change from NAVA₂ to SIMV₂ (and for the other group starting with SIMV₁ until NAVA₂) of total, right / left and upper / lower impedance. A Shapiro-Wilk one-sample test was performed to evaluate the normal distribution of all cumulative and singular parameters. Normally-distributed values were compared by using the Student's t-test. For comparison of multiple, non-normally distributed variables, the Mann-Whitney U Test was performed. To calculate the statistical significance of the relative differences between ventilation modes, a Wilcoxon-test was used. A test variable of "1" was applied to account for the null-hypothesis of expecting no difference of the two measured impedances between both ventilatory modes. The computed relative differences of impedance data were compared with regard to applied electrodes via a two-sample Wilcoxon-test. Simultaneously recorded ventilation settings during NAVA and SIMV

sequences were compared via a two-sample Student's t-test to detect any difference in ventilatory conditions. A one-way analysis of variance (ANOVA) in combination with a Tukey's post-hoc correction was used to determine differences of impedance when changing the ventilation from NAVA to SIMV (PC) PS in each child. A p-value of < 0.05 indicated statistical significance.

Results

Altogether eight children fulfilled the inclusion criteria for continuation in the electrical impedance segmentographic measurements. Demographic data is depicted in Table 1.

Table 1
Demographic data.

n	age(d)	sex	weight(g)	diagnoses	reason for admission	MV(d)	PICU(d)
1	65	f	5100	infusothorax	s/p CPR	8	8
2	104	m	4200	respiratory failure	hypertrophic cardiomyopathy	1	1
3	5	m	3480	postoperative, cardiac	Ebstein anomaly	6	2
4	208	m	6600	sepsis with ARDS	coarctation of the aorta	16	25
5	20	m	3100	postoperative	Fallot tetralogy	6	6
6	73	m	3900	postoperative	atrioventricular septal defect	1	1
7	9	f	3500	respiratory failure	meconium aspiration syndrome	9	9
8	27	m	3000	postoperative	restrictive cardiomyopathy	10	10
M (IQR)	46 (12–96)		3700 (3195–4875)			7 (1.75–9.25)	7 (2.25–9.25)

n, patient identification number; d, days; g, gram; MV, length of mechanical ventilation before the study; PICU, length of stay at the intensive care before initiation of the study; f, female; s/p, status post; CPR, cardiopulmonary resuscitation; m, male; ARDS, acute respiratory distress syndrome; M, median; IQR, interquartile range. Underlined numbers represent children with evaluable results of segmental impedance data.

Designed as a prospective crossover study, one of two groups, consisting of three children, started ventilation on NAVA, while five children were started on SIMV (PC) PS. Figure 2 shows a real-time user

interface of the Angelie[™] EIS system, depicting percentage share of distribution of segmental electric impedance and main ventilatory parameters. Individually-measured electric impedance values are given as arbitrary units (a.u.). Measured a.u. showed high variability in total electric impedance (median 435 a.u., IQR 186–1461 a.u.) with a median segmental impedance division of the upper left (UL) segment of 19% (IQR 1–32%), the upper right (UR) of 8% (IQR 1–17%), the lower left (LL) of 21% (IQR 15–37%) and the lower right (LR) segment of 33% (IQR 14–56%). By performing a one-sample Shapiro-Wilk test, the distribution of relative difference of impedance, secondary to the ventilation mode, was assessed, whilst a p-value greater than 0.05 had been expected to distinguish normal distribution. A normal distribution of data was found in vertical and horizontal impedance, independent of ventilation mode or change during all crossovers (Table 2).

Table 2
Distribution of relative difference of impedance.

		p-value
total impedance	total	0.00
	change1	0.00
	change2	0.04
	change3	0.04
vertical impedance	total	0.28
	change1	0.28
	change2	0.19
	change3	0.46
horizontal impedance	total	0.11
	change1	0.11
	change2	0.12
	change3	0.30
Results of a one-sample Shapiro- Wilk test. A p-value greater than 0.05 was expected to distinguish normal distribution.		

Relative difference of impedance performed by butterfly electrodes showed normal distribution throughout all measurements in total (total p = 0.24, vertical p = 0.90, horizontal p = 0.84) and crossovers. Using single electrodes, all total values of both (p = 0.02) horizontal (p = 0.03) and vertical impedance were not normally distributed (p = 0.001). In three of the eight children, more than one of the segmental impedance values in one or more sequences showed less than four percent of total impedance. As these three children had undergone cardiac surgery, the use of butterfly electrodes was not applicable due to median thoracotomy. In the remaining five children, only one had been thoracotomized and was

measured by using single electrodes (Table 1). When omitting impedance data of the aforementioned three children, with little or no segmental data, median segmental impedance division amounted to 26% (IQR 22–39%) of the UL, 16% (IQR 5–19%) of the UR, 20% (IQR 15–28%) of the LL and 33% (IQR 15–37%) of the LR segment. A difference of acquired data between single and butterfly electrodes was found when measuring cumulative horizontal impedance ($p = 0.05$, Table 3).

Table 3

Median of the relative differences between all sequences and variables depending on the type of electrode.

		butterfly electrodes	single electrodes	
		m (IQR)		p-value
total impedance	total	0.75±(0.50–1.45)	1.42±(0.22–4.49)	0.86
	change1	0.75±(0.51–0.81)	0.23±(0.15–3.19)	1.00
	change2	0.89±(0.48–1.88)	1.06±(0.13–4.13)	0.29
	change3	1.12±(0.53–2.29)	3.05±(1.37–6.65)	0.59
vertical impedance	total	0.69±(0.55–0.96)	0±(0-0.42)	0.77
	change1	0.69±(0.54–0.89)	0±(0-1.04)	0.11
	change2	0.80±(0.55–1.43)	0±(0-0.35)	0.11
	change3	0.78±(0.55–1.26)	0.13±(0-1.51)	1.00
horizontal impedance	total	0.90±(0.85–1.25)	1.00±(0.22–1.30)	0.05
	change1	0.96±(0.76–1.27)	1.08±(0.24–1.29)	0.59
	change2	0.92±(0.85–1.41)	1.10±(0.22–2.70)	1.00
	change3	0.87±(0.55–1.22)	1.00±(0.25–1.17)	0.59

Data is presented as median (interquartile range).

The mean weight of the remaining five children was 4660 ± 1234 grams (g). Mean weight of the other three children lacking segmental impedance data was lower in comparison (mean 3193 ± 253 g, $p = 0.04$). After omitting data of the three children lacking segmental data, a difference in total transthoracic impedance during the first change of NAVA and SIMV was obtained (median 0.70, IQR 0.36–0.81, $p = 0.02$). The remaining total, horizontal and vertical data showed no differences in electrical impedance. Data of total impedance showed no differences concerning change of ventilatory modes, neither after the first, second or third changes between NAVA and SIMV (PC) PS (Fig. 3). The observations of horizontal impedance were similar (Fig. 4). A difference of vertical impedance, however, was found both after the

first (0.58 IQR 0-0.89; $p = 0.04$) and second ventilatory mode changes (0.50 IQR 0-0.88; $p = 0.05$), as well as of the total impedance (0.52 IQR 0-0.87; $p = 0.002$, Fig. 5). In comparison, regardless of the first ventilatory mode in this crossover design, no differences in impedance were detected (total impedance, $p = 0.68$; vertical impedance, $p = 0.26$; horizontal impedance, $p = 0.68$). ANOVA showed no impact of the ventilation mode in a.u. of total electrical impedance ($F(3.28) = 0.4572$, $p = 0.71$). Nor did the ventilatory mode impact the percentage of left ($F(3.28) = 0.2849$, $p = 0.84$) or the percentage of upper impedance ($F(3.28) = 0.2456$, $p = 0.86$). The comparison of the ventilation settings between NAVA and SIMV (PC) PS showed no differences for V_T ($p = 0.54$), frequency ($p = 0.207$), PEEP ($p = 0.18$) or minute volume ($p = 0.45$, Table 4).

Table 4
Ventilatory parameters during NAVA and SIMV (PC) PS.

	ventilation mode	median (IQR)	p-value
V_T (ml)	SIMV	22.1 (17.5/46.2)	0.540
	NAVA	24.4 (15.4/35.1)	
RR (per min)	SIMV	38 (22.25/44.75)	0.207
	NAVA	38.5 (29.25/53)	
PEEP (mbar)	SIMV	4.9 (4.7/5.5)	0.188
	NAVA	5.1 (4.8/5.6)	
MV (ml/min)	SIMV	888 (557.9/1342.2)	0.453
	NAVA	837.4 (657.1/1099.2)	

V_T , tidal volume; SIMV, synchronized intermittent mechanical ventilation; NAVA, neurally adjusted ventilatory assist; RR, respiratory rate; PEEP, positive end-expiratory pressure; MV, minute volume.

Altogether, a difference in vertical electrical impedance was detected when switching between NAVA and SIMV (PC) PS. This effect was detected in all measured impedances, as well as during the first and second change of ventilation mode.

Discussion

Performed as a prospective case-control crossover trial of NAVA and SIMV (PC) PS, differences of impedances were assessed by segmentography using the Angelie[→] device. Ventilatory monitoring has been mainly limited to overall information and radiation-associated imaging methods without real-time information of regional dynamic lung mechanism. Therefore, as a bedside tool, the Angelie[□] segmentography device is simple to implement in children; causing no distress during electrode placement or skin irritation. As a case-control trial, each child served as its own control to reduce interpersonal differences. By further performing a crossover of NAVA and SIMV (PC) PS, potential

influences of each initial ventilation mode were presumably diminished. Recruitment of dependent lung areas during spontaneous ventilation has been documented by various authors (18, 19). Our study design allowed for conclusions to be drawn from the reduction and vertical shift of impedance from transthoracic to lower lung segments during NAVA in comparison to SIMV (PC) PS. This effect has shown to be particularly pronounced in NAVA ventilation, by improved patient-ventilator synchronization, which can be attributed to a neurally-driven trigger mechanism.(4, 8–10, 20) However, it could also be assumed that this shift of impedance was exaggerated due to the lack of segmental data in some children. When excluding data measured by single electrodes, the aforementioned vertical shift was shown to be less pronounced. In our analysis, neither V_T , PEEP or minute volume differed between NAVA and SIMV (PC) PS. Documented ventilatory settings of this present study, therefore, were comparable to a recent study by Baez Hernandez et al that reported no change of V_T during NAVA ventilation(4). However, other interventions comparing NAVA and conventional ventilation in pediatric patients have reported decreased PIP levels on NAVA.(17, 20, 21) Some authors have described reduced V_T in NAVA-ventilated children (17) and increased respiratory rates when compared to pressure-supported ventilation.(21) Ventilation mode did not seem to impact total electrical impedance in our study. Furthermore, no differences in total, vertical or horizontal impedance were detected irrespective of whether NAVA or SIMV (PC) PS was the first ventilation mode. Throughout all crossover sequences, no differences in total impedance concerning ventilation modes were observed. However, there was a difference in vertical impedance after the first and second changes between NAVA and SIMV (PC) PS. Summarizing these results, measured by a case-control trial with a crossover of two ventilation modes, electrical impedance segmentography did not appear to reliably measure changes of impedance between NAVA and SIMV (PC) PS, as various studies have also shown performing different methods.(17, 22, 23) A recent study utilizing the same EIS monitoring system on healthy, non-sedated and spontaneously-breathing infants reported technical and clinical difficulties in obtaining reliable impedance measurements and described a high patient dropout of 33%.(14) Children of our current study, however, were all intubated and sedated; hence, individual measurement biases, such as movement, could be ruled out. Nevertheless, impedance segmentography has shown to be a useful tool in spontaneously-breathing four year-olds with bronchopulmonary dysplasia for segmental evaluation after inhalation of salbutamol.(24) Nevertheless, singular segmental impedance data was not consistently measurable in our cohort. Data was particularly lacking when measuring the apical sections. In upper right segments, electrical impedance could only be measured in half of our children. By its crossover design, initial data from three children with few or no segmental measurements in the calculation of relative differences were included. When excluding these children from the analysis, in whom at least two segments accounted for less than four percent of total impedance, a segmental shift of distribution in impedance was found, similar to the results of Reiterer et al.(14) Optimal placement of the electrodes, therefore, should be highlighted since the lack of a segmental impedance measurement was potentially caused by the use of single electrodes. The butterfly electrode ensures equal distance between each of the incorporated electrodes. Since half of our study population previously underwent extensive heart surgeries, only single electrodes could be used. In these patients, the central electrode was placed on one side (on the left side) of the scar. Therefore, interference with correct and comparable measurements cannot be ruled out completely as the measuring area

appears to be displaced (Fig. 5). On the other hand, it should be mentioned that only one size of butterfly electrodes are available. Size-adjusted electrodes for different patients would be preferable to increase accuracy of segmental data. By not excluding patients with measurements performed by single electrodes, it could be shown that the application of butterfly electrodes is limited in indication and children's size. Furthermore, this also underlines the limitation of the use of single electrodes due to a potentially altered measuring area. Further, segmentography data performed by Angelie[□] could mainly be measured in children weighing more than 3500 grams. One reason for this could be the amount of lung tissue between segmental electrodes, allowing a more distinctive differentiation between each sector and minimizing interference. Increased V_T might be the leading cause of these lack of measurements. In contrast to EIS, EIT provides impedance changes of the cross-section of the thorax. Studies of EIT have provided highly-reliable impedance data; also in smaller infants.(13, 25) Although our study population in relation to age and weight, as well as the median days of PICU stay were inhomogeneous, it should be pointed out that all children underwent the same length of intervention. On the basis of a sensitive study population, the time period of intervention for each child was kept to a minimum. Applied and investigated ventilation techniques, however, are known to be clinically beneficial when patients are ventilated for longer periods.(2, 8, 10) For patients requiring long-term ventilation, EIS may therefore be a useful device for dynamic continuous monitoring. Immediate benefits of personalized ventilatory strategies can result when using this simple-to-apply bedside tool measuring lung impedance.

Conclusion

Using Angelie[→] as an EIS monitoring tool enables dynamic monitoring for transthoracic impedance during ventilation of children. Measurements of singular segmental lung areas, however, were of low reproducibility due to various limiting factors in the device's application. Additional prospective randomized trials with a larger number of pediatric patients are needed for further investigation on the reproducibility of segmentographic impedance measurements.

Abbreviations

AC alternating current

a.u. arbitrary units

ARDS acute respiratory distress syndrome

CPR cardiopulmonary resuscitation

E_{adi} Electrical activity of the diaphragm

EIS Electric Impedance Segmentography

EIT Electrical Impedance Tomography

g gram

IQR interquartile range

LL lower left

LR lower right

NAVA Neutrally Adjusted Ventilatory Assist

NICU neonatal intensive care unit

PEEP positive end expiratory pressure

PICU Pediatric Intensive Care Unit

PIP positive inspiratory pressure

SIMV (PC) PS Synchronized intermittent pressure controlled and breath supported mandatory ventilation

UL upper left

UR upper right

V_T tidal volume

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of Medical University of Vienna (EK No 1668/2018). All performed procedures in this study were in accordance with the ethical standards of the institutional review board and with the Helsinki declaration of 1964. Informed consent was obtained by all care givers of the patients before inclusion to the study.

Consent for publication

Not applicable.

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare no competing interest related to this data. The authors have no financial relationships relevant to this article to disclose.

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Authors' Contributions

J.B.B. and A.M. performed the drafting of the manuscript and developed the research strategy. A.M. and M.H. contributed data collection. J.B.B., A.M., T.W. and M.H. analyzed and interpreted the data. J.B.B, A.M. and T.W. performed the statistical analysis of the data. J.B.B., A.M., T.W., R.U. and M.H. critically edited and revised the manuscript. All authors read and approved the final manuscript.

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Figures

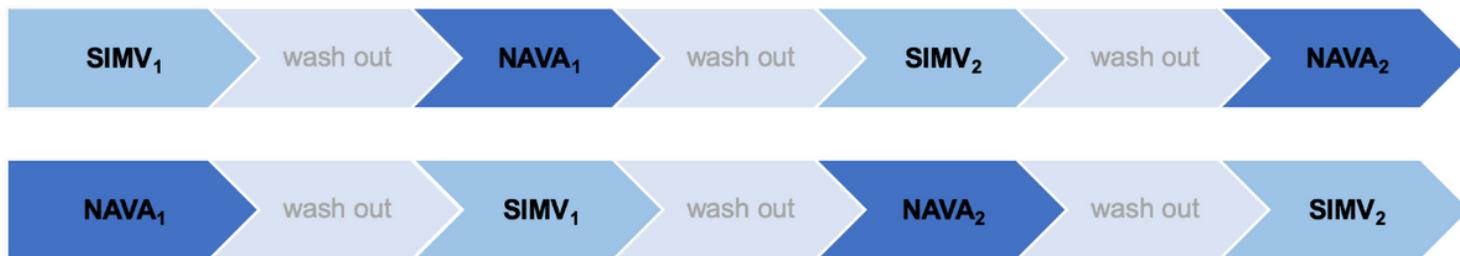


Figure 1

Crossover of neurally adjusted ventilatory assist (NAVA) and synchronized intermittent mandatory ventilation (SIMV).

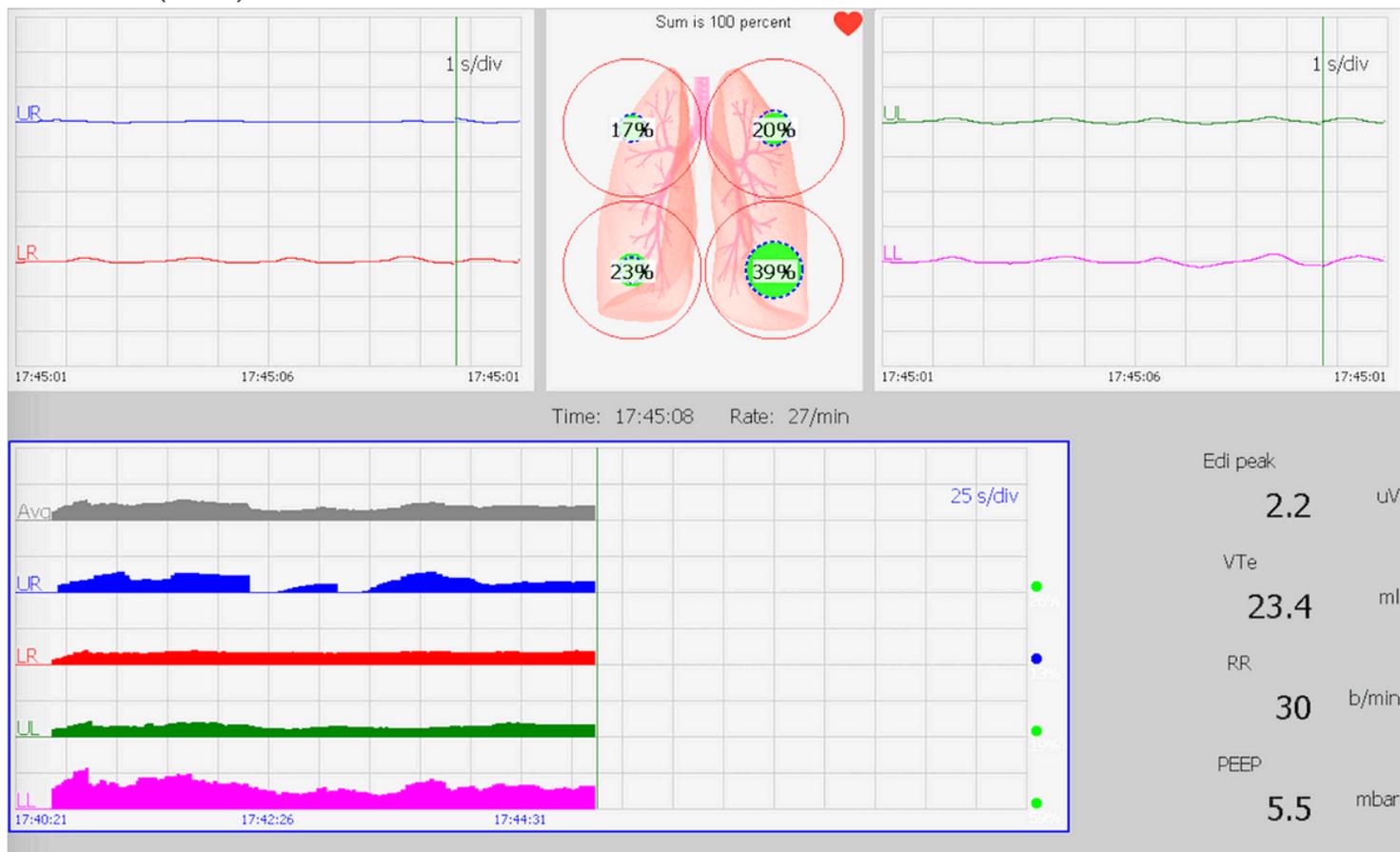


Figure 2

Real-time user interface of the Angelie® EIS system.

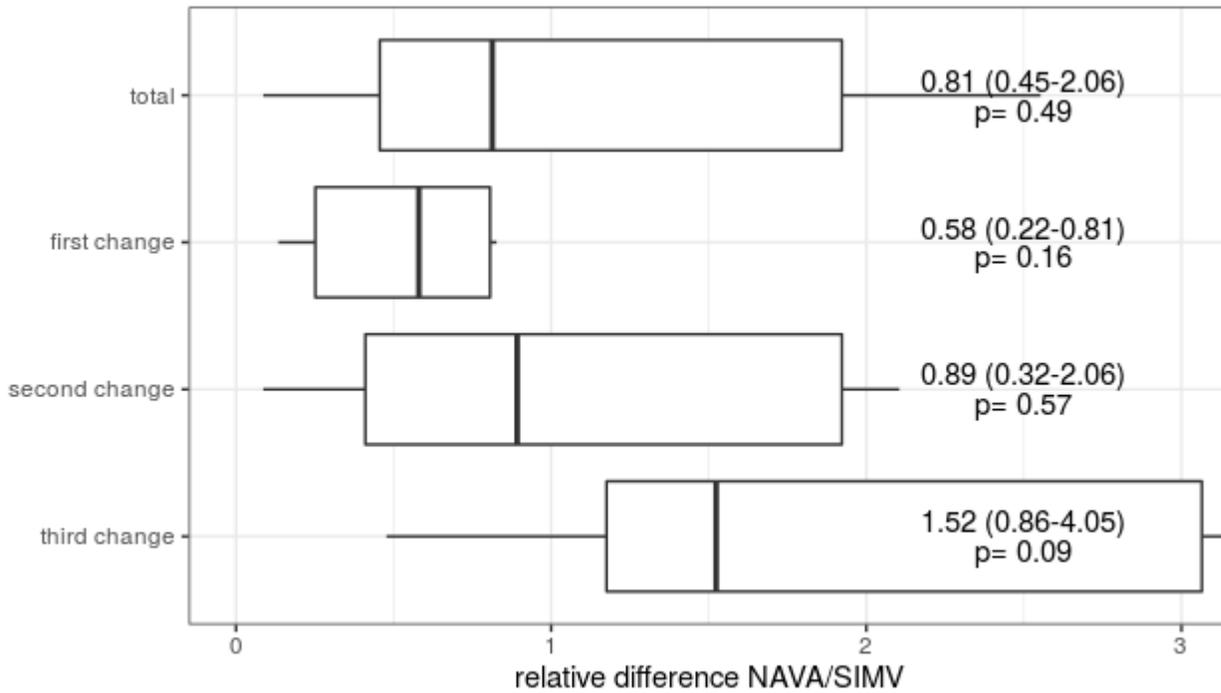


Figure 3

Cumulative and singular total impedance shift depending on the applied breathing mode.

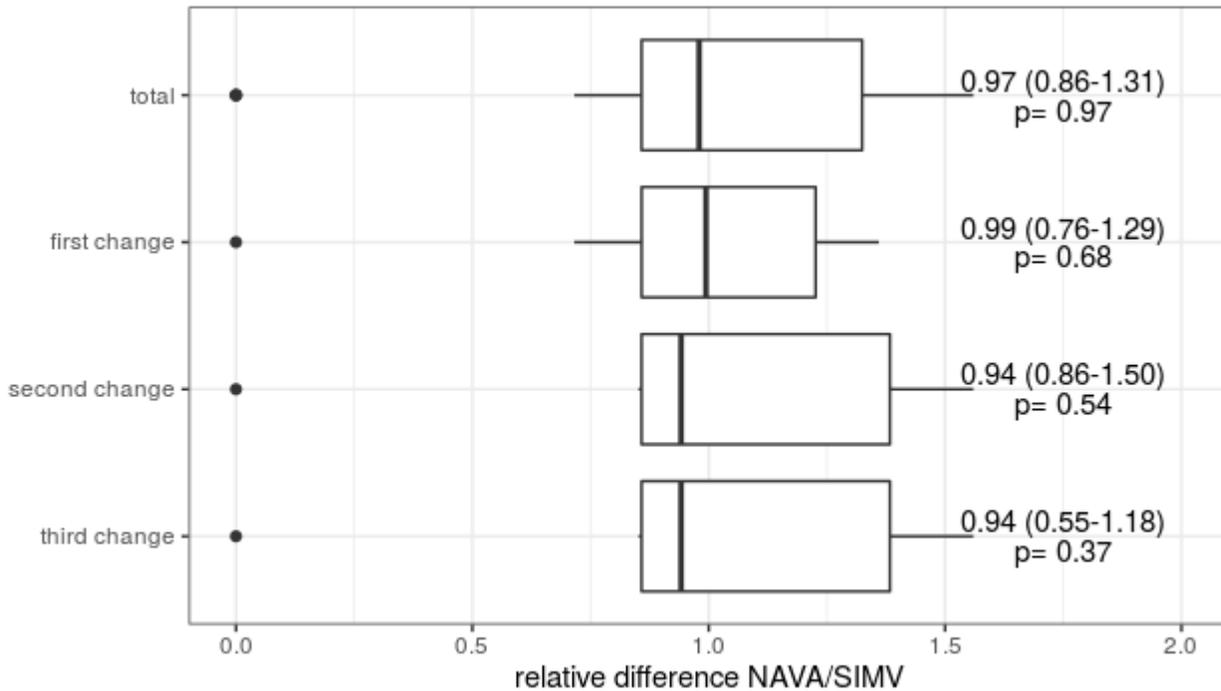


Figure 4

Cumulative and singular impedance shift of the percentage of the left segments depending on ventilatory mode.

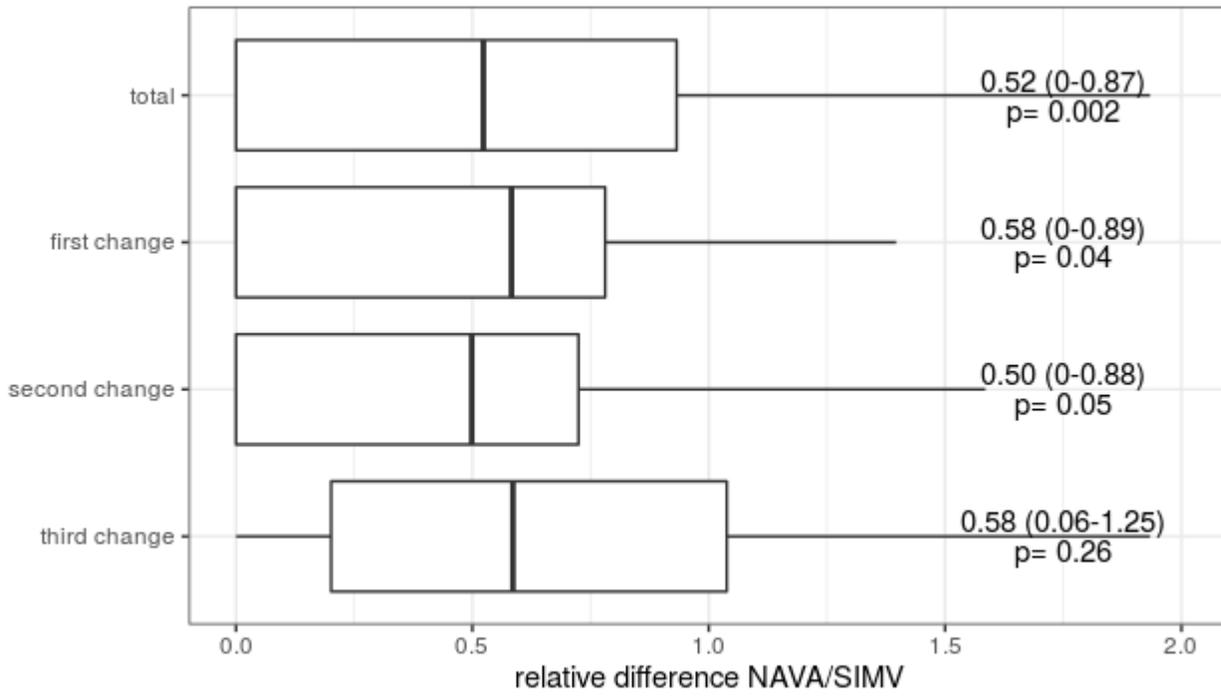


Figure 5

Cumulative and singular impedance shift of the percentage of the upper segments depending on the applied breathing mode.

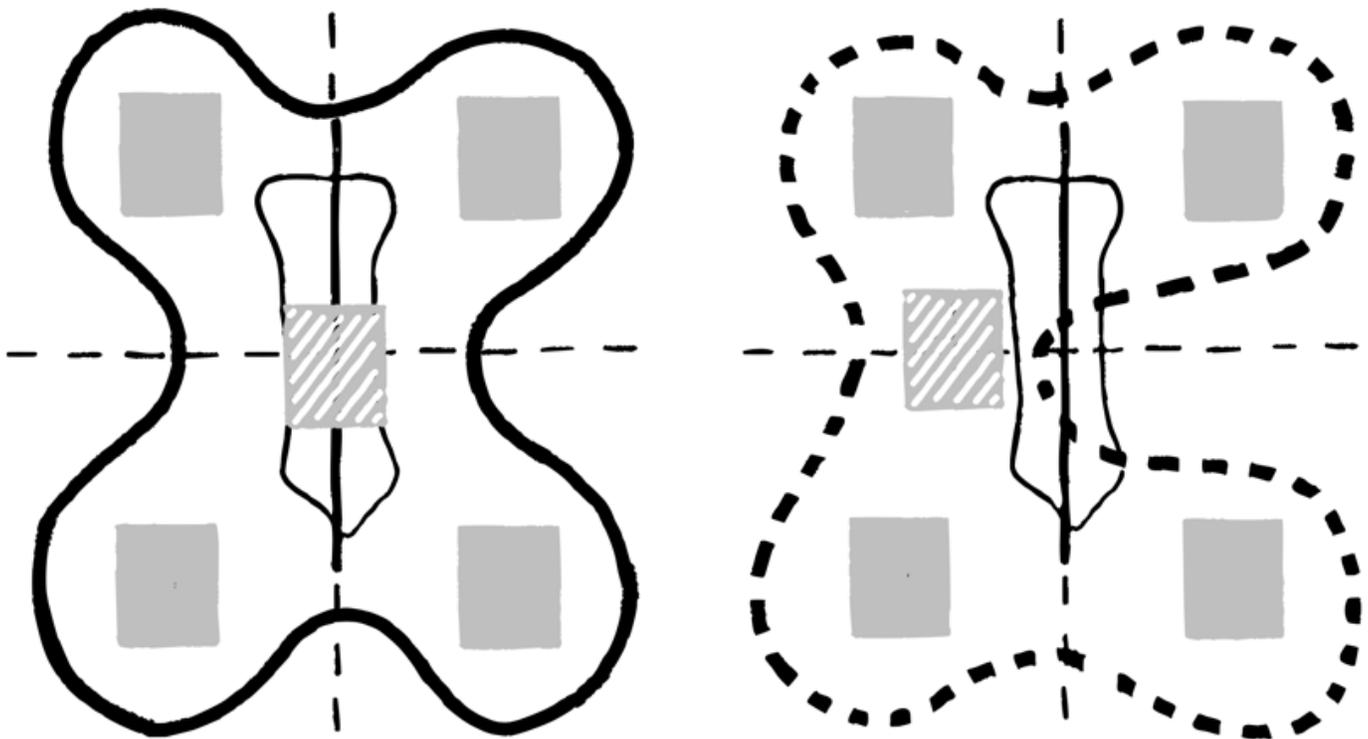


Figure 6

Measuring area of butterfly and single electrodes.

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