

## PROSPECTIVE STUDY COMPARING SKIN IMPEDANCE WITH EEG PARAMETERS DURING THE INDUCTION OF ANAESTHESIA WITH FENTANYL AND ETOMIDATE

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### Abstract

**Objective:** Sympathetic stimulation leads to a change in electrical skin impedance. So far it is unclear whether this effect can be used to measure the effects of anaesthetics during general anaesthesia. The aim of this prospective study is to determine the electrical skin impedance during induction of anaesthesia for coronary artery bypass surgery with fentanyl and etomidate.

**Methods:** The electrical skin impedance was measured with the help of an electro-sympathicograph (ESG). In 47 patients scheduled for elective cardiac surgery, anaesthesia was induced with intravenous fentanyl 10 µg/kg and etomidate 0.3mg/kg. During induction, the ESG (Electrosympathicograph), BIS (Bispectral Index), BP (arterial blood pressure) and HR (heart rate) values of each patient were recorded every 20 seconds. The observation period from administration of fentanyl to intubation for surgery lasted 4 min.

**Results:** The ESG recorded significant changes in the electrical skin impedance after administration of fentanyl and etomidate ( $p < 0.05$ ). During induction of anaesthesia, significant changes of BIS, HR and blood pressure were observed as well ( $p < 0.05$ ).

**Conclusions:** The electrical skin impedance measurement may be used to monitor the effects of anaesthetics during general anaesthesia.

**Key words:** skin impedance, general anaesthesia, fentanyl, etomidate, cardiac surgery

### INTRODUCTION

Clinical assessment uses parameters such as heart rate and blood pressure to determine anaesthetic depth. Administration of etomidate in combination with fentanyl has been suggested for induction of anaesthesia in high-risk patients for cardiac surgery, because of their minor cardiovascular effects [1]. The partly opposed effects of etomidate and fentanyl on heart rate and blood pressure do not allow to predict the adequacy of anaesthesia on the basis of these parameters [2,

3, 4]. This is particularly the case in cardiac high-risk patients, whose heart rate and blood pressure behaviour are often dictated by the underlying heart impairment and by heart medication. Cardiosurgical operations are considered to bear a higher risk of unintended intraoperative awareness compared to general surgical operations [5].

A previous study addressing EEG changes during a cardiosurgical operation with postoperative recall found no relationship between the time spent awake and EEG changes [6]. In addition, Barr and colleagues observed an insufficient correlation between bispectral index and intraoperatively measured plasma midazolam and fentanyl levels and clinical assessment of anaesthetic depth in 10 cardiosurgical patients [7]. In a study targeting the induction of anaesthesia using fentanyl in cardiosurgical patients, the same authors came to the conclusion that the BIS monitor is not capable to measure the hypnotic effects of fentanyl [8].

In a further study dealing with assessing anaesthetic depth by means of skin conductance measurements, the state of activity of the sympathetic nerve system was predicted with the help of the eccrine sweat gland duct filling. For this purpose, the authors measured the changes in a parameter called NSCF (number of skin conductance fluctuations). This parameter that correlates directly with bursts in the skin sympathetic nervous system was suggested to be an indicator of the analgesic effects of opioids during general anaesthesia [9].

Opiates, just like narcotics, act through central mechanisms thereby damping the activity of the sympathetic system, followed by changes in skin impedance. The aim of the present prospective study was to investigate the effects upon skin impedance of an intravenous bolus of fentanyl, which was given without previous administration of hypnotics, and a subsequent etomidate bolus.

For this purpose, the electrosympathicograph (ESG) was used to measure the changes in skin impedance in patients undergoing elective cardiac surgery.

## METHODS

## PATIENTS

47 patients (ASA III), who were undergoing elective cardio-surgical intervention, were studied prospectively. Approval for the study was given by the local Medical Ethics Committee. All patients gave their written informed consent prior to being enrolled into the study.

Patients aged under 18 yr were excluded, as were those with neurologic or psychiatric diseases, intake of psychoactive medication, abuse of drugs or alcohol, skull-brain trauma in the patient's medical history, and hearing disorders.

Table 1. Participants characteristics.

Gender (Male/Female), (n)	34 / 13
ASA III (n,%)	47, 100
Age (yr)	59 ± 17
Height (cm)	170 ± 27
Weight (kg)	79 ± 18

Data shown as mean ± SD unless otherwise indicated

## STUDY AND TEST PROCEDURES

All study measurements were carried out in an anaesthesia induction room patients laying on supine on an operation table. Prior to induction of anaesthesia, an invasive blood pressure measurement system via the arteria radialis was established, a venous catheter and a pulse oximeter were placed and an ECG (electrocardiogram) was administered. The invasively measured blood pressure and heart rate were stored directly online in a computer file with the assistance of the program AS3 collect (Datex-Ohmeda S/5 Anaesthesia Monitor System). All study participants were continuously administered 4 liters of O<sub>2</sub> through a nasal probe. A BIS electrode (BIS Sensor XP) for BIS monitoring was attached to the forehead in accordance with the specifications from the manufacturer. As for ESG monitoring, 2 ECG electrodes were fastened to the palm (2<sup>nd</sup> and 3<sup>rd</sup> finger) of the non-dominating hand. The timers of the S/5 Anaesthesia Monitor System, BIS Monitor and ESG were synchronised prior to beginning the measurements. A serial cable was connected to both the BIS monitor and a laptop in order to enable continuous recording of the BIS values; the laptop stored the data in a text file with the help of the Microsoft Hyperterminal program. The ESG used a continuous real-time automatic online process to store the measured skin impedance data in a computer file over the entire period of time.

At the beginning of the observation period, baseline measurements of ESG, BIS, BP and HR values were recorded. Thereafter, the patients received 1.0 µg/kg intravenous fentanyl. 160 seconds after administration of fentanyl, the patients were injected with additional 0.3 mg/kg of etomidate. After the loss of eyelash reflex, patients were ventilated through an oxygen mask and pancuronium 0.1 mg/kg was given to facilitate tracheal intubation. The study period lasted

from the time of administration of fentanyl up to the time of intubation (approximately four minutes).

## ESG AND BIS MEASUREMENTS

Skin impedance measurements were performed with the help of an electrosympathicograph (ESG) (ESG 1001 Monitor System, Dr. Janitzki Consulting Engineers, Altenbeken, Germany). The measurement was made in the constant direct current mode with the help of Ag/AgCl electrodes that were applied to a small skin area at a current density of < 2 µA/cm<sup>2</sup>. Every 200 ms (5 HZ), the impedance data were periodically recorded in real time [10], underwent analog signal processing and filtering, and were then transmitted to an analog-to-digital converter. The very large measurement range demanded that an analog-to-digital converter having a resolution of 18 bits plus sign be used. In order to not leave the measurement data susceptible to failure, digitization was done as soon as possible. Opto-couplers then transferred the digital data to a computer for further processing.

This computer predominantly fulfills three tasks: it organizes and controls the recording of the measurement data (likewise via optocouplers), performs the digital processing of the recorded measurement data and displays them on a monitor screen. Thirdly, the computer performs a quasi-continuous recording (every 0.2 seconds) of all digital measurement data in a non-volatile storage medium (storage space requirements: ca. 100 KByte per hour and channel). The data so stored can be exactly assigned to each single measurement and to a specific time, which allows them to be used by other computers and programs in a later processing.

The system's measurement range spans from 5000 Ω to 2,000,000 Ω. It is also possible to perform measurements below 5000 Ω, but then the measurement sensitivity is strongly reduced, and the temperature dependence of the sensors increases. Changes of up to 100 Ω are in the normal sensitivity range. The baseline impedance values on the insides of the hands are in the range from 10,000 Ω up to several 100,000 Ω.

Available skin impedance recording electrodes included standard ECG solid gel surface electrodes having a recording surface of 2.2 cm<sup>2</sup>, and consisting of a 5% KCl conductive adhesive gel (Conmed - 1700 Cleartrace; Conmed Deutschland GmbH, Gross-Gerau, Germany).

The skin impedance monitor (ESG) records 5 measurement values per second. While the measurements are being made, the measurement data appear graphically on the monitor screen in the form of a tonic electrosympathicogram (tonic ESG) in a time function as ESG measurement curve expressed in KΩ (Kilo Ohm). These measurement values appear online in a diagram directly on the monitor screen without having undergone additional pre-processing. The tonic ESG measurement value in KΩ is updated every 5 seconds and shown in a numeric display. The method was recently published [11, 12].

For determination by bispectral analysis we used an A- 2000 BIS monitor (software version 3.3, Aspect Medical Systems, Newton, MA, USA). Every five sec-

onds the Aspect 2000 BIS monitor delivers a new bispectral analysis, which is calculated retroactively from the past 15 seconds. For us to be able to do a statistical evaluation, BIS, ESG, blood pressure and heart rate values were taken every 20 seconds from the time of administration of fentanyl up to the time of intubation. Two investigators read all measurement values directly from the monitor screen and entered them into a previously developed test protocol. Prior to statistical analysis, all values entered by hand were examined for accuracy; this was achieved by comparing them to the values recorded online.

STATISTICAL ANALYSIS

The statistical evaluation served the purpose of identifying possible correlations between skin impedance data and time and BIS values.

Possible temporal changes in ESG values were identified using the multivariate analysis of repeated measurements, a specific analysis method for time-dependent data. The time-dependent effect was quantified using Wilks' Lambda.

In addition to the absolute ESG values, any changes in the ESG values compared to the baseline value were also determined using the following two formulae:  $RESG(t_x) = [ESG(t_x) - ESG(t_0)] / ESG(t_0)$ . And  $DESG(t_x) = ESG(t_x) - ESG(t_0)$

[ $RESG(t_x)$  = relative change in ESG at the time of measurement;  $ESG(t_x)$  = ESG at the time of measurement;  $ESG(t_0)$  = ESG at baseline time point;  $DESG(t_x)$  = change in ESG at the measurement time point].

This enables to look only at the course of the ESG values, independently of different absolute values.

The paired t-test compared the parameters (BIS, ESG) during their time course after administration of fentanyl and etomidate. Another operation that was done included computing Pearson's correlation coefficients between BIS and ESG values at the individual measurement time points.

A value of  $p < 0.05$  was considered statistically significant. Statistical evaluation was done with the assistance of the SPSS program for Windows, version 14.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Relevant complications were not observed in any study participant. During the observation period, no patient experienced a decrease in peripheral saturation below 90. All 47 patients were intubated and mechanically ventilated at the end of the observation period. Thereafter, the surgical intervention was performed as planned. The observation period lasted 280 s for each patient

160 seconds after fentanyl administration, the heart rate had fallen significantly from  $75 \pm 15$  to  $70 \pm 16$  1/min ( $p = 0.04$ ). Administration of etomidate produced a significant rise in heart rate within 120 seconds, namely from  $70 \pm 16$  to  $74 \pm 19$  1/min ( $p = 0.0001$ ). (Fig. 1). At the time of intubation, the heart rate showed another rise to  $77 \pm 20$  1/min. 160 seconds after the administration of fentanyl, the mean blood pressure had fallen significantly from  $96 \pm 19$  to  $86 \pm 23$  mmHg ( $p = 0.009$ ). A significant change in

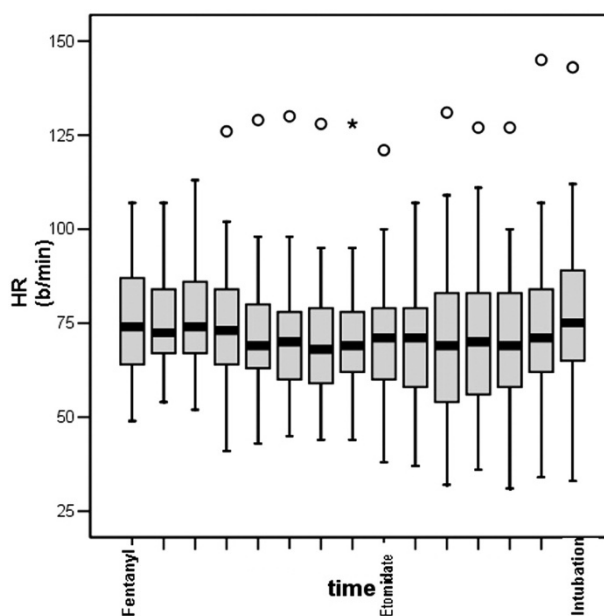


Fig. 1. HR during induction of Anaesthesia. Boxes indicate median and 24<sup>th</sup>-75<sup>th</sup> percentiles, whiskers the range.

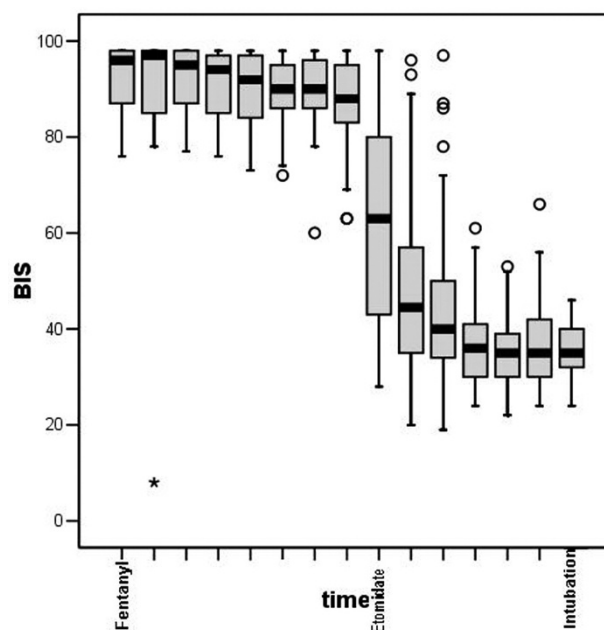


Fig. 2. BIS index during induction of Anaesthesia. Boxes indicate median and 24<sup>th</sup>-75<sup>th</sup> percentiles, whiskers the range.

blood pressure was also observed after administration of etomidate. At first, mean blood pressure fell from  $86 \pm 19$  to  $77 \pm 18$ , and then it rose to be  $87 \pm 23$  at the time of intubation ( $p = 0.005$ ). This elevation in blood pressure was caused by an early administration of noradrenaline in order to maintain sufficient coronary perfusion pressure.

Following administration of fentanyl, the bispectral index changed significantly from  $93 \pm 6$  to  $87 \pm 10$  ( $p = 0.036$ ). During the time that elapsed from etomidate administration until intubation, the bispectral index value fell highly significantly from  $62 \pm 21$  to  $36 \pm 6$  ( $p < 0.001$ ) (Fig. 2). Administration of fentanyl also

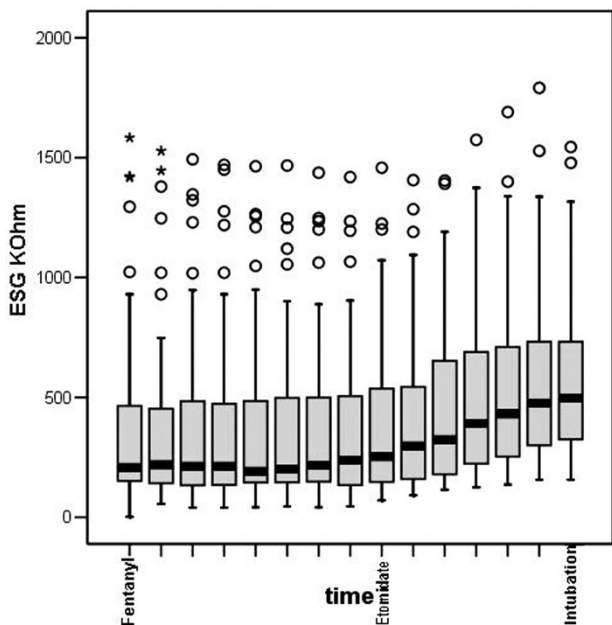


Fig. 3. ESG during induction of Anaesthesia. Boxes indicate median and 24<sup>th</sup>-75<sup>th</sup> percentiles, whiskers the range.

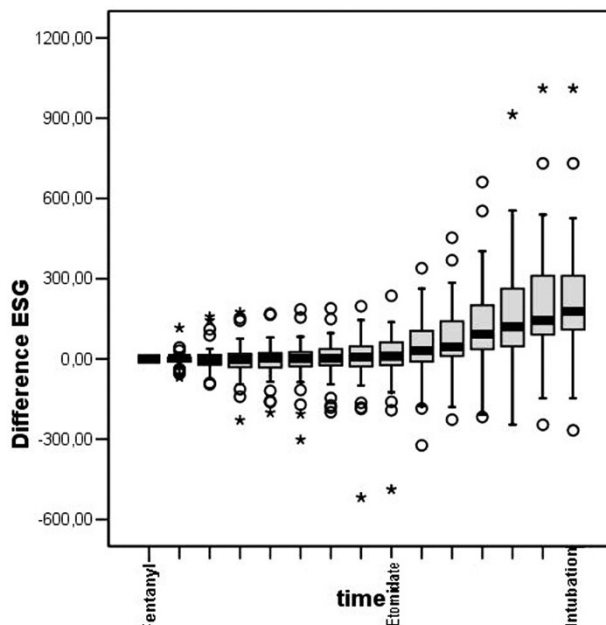


Fig. 4. Difference ESG during induction of Anaesthesia. Boxes indicate median and 24<sup>th</sup>-75<sup>th</sup> percentiles, whiskers the range.

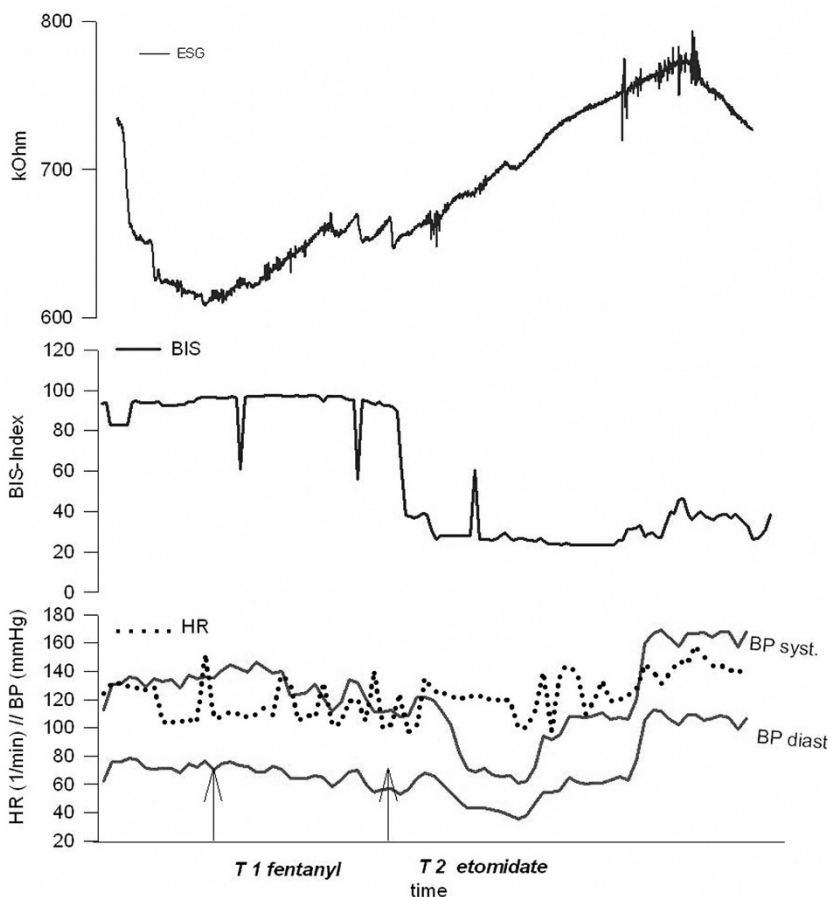


Fig. 5. Original curves of a patient during induction of Anaesthesia.

produced a significant change in spectral edge frequency, namely from  $20 \pm 7$  to  $18 \pm 6$  ( $p = 0.03$ ). After etomidate injection, it fell highly significantly to  $14 \pm 2$  ( $p = 0.0001$ ).

Within 160 seconds after administration of fentanyl, the skin impedances measured by the ESG exhibited a

broad spread due to the high degree of variance between the baseline values. The average values fluctuated from  $378 \pm 441$  k $\Omega$  at the time of the injection of fentanyl, to  $374 \pm 348$  k $\Omega$  160 seconds after the injection (Fig. 3) That is why also the changes in ESG values with respect to the baseline values were looked at

in addition to the absolute ESG values. After injection of fentanyl, there was a significant change in the relative difference of the ESG values ( $RESG_{t_x}$ ) from  $2.5 \pm 17$  to  $3.3 \pm 22$  ( $p = 0,021$ ). After injection of etomidate, the course of the ( $RESG_{t_x}$ ) values demonstrated a highly significant change from  $3.1 \pm 20$  to  $17 \pm 107$  (Fig. 4). Even the absolute ESG values exhibited a highly significant change after infusion of etomidate; despite their broad spread they fluctuated from  $388 \pm 345 \text{ k}\Omega$  to  $595 \pm 361 \text{ k}\Omega$ . ( $p = 0.0001$ ) (Fig. 3).

Pearson's Correlation at the individual measurement time points measured a significant (negative) correlation relationship between the absolute ESG values and BIS values at the beginning ( $r = -0,3$ ;  $p = 0.04$ ), 40s ( $r = -0,4$ ;  $p = 0.005$ ), 60s ( $r = -0,3$ ;  $p = 0.02$ ), 80s ( $r = -0,3$ ;  $p = 0.04$ ), 100 s ( $r = -0,3$ ;  $p = 0.02$ ), and 120s ( $r = -0,4$ ;  $p = 0.03$ ), after the injection of fentanyl. Administration of etomidate resulted in a significant (negative) correlation between the ESG difference values ( $DESG_{t_x}$ ) and the BIS values at the measurement time points of 0s ( $r = -0,3$ ;  $p = 0.03$ ), 20s ( $r = -0,3$ ;  $p = 0.03$ ) and 40s ( $r = -0,4$ ;  $p = 0.02$ ).

Baseline skin impedances varied greatly among study participants. This provides the explanation for the broad spread among the ESG values. Generally, the skin impedances rose after injection of fentanyl, and BIS values decreased. After etomidate administration, the skin impedances took a steep increase whereas the BIS values underwent a considerable fall. The paired t-test revealed highly significant changes both for the ESG difference values ( $DESG_{t_x}$ ) and for the BIS values ( $p < 0.001$ ) in a direct comparison of the individual time intervals following administration of fentanyl and etomidate. See blood pressure, BIS and ESG original curves of a patient during induction of anaesthesia (Fig. 5).

## DISCUSSION

The results of this study show the course of skin impedances measured by the ESG during induction of cardio-surgical anaesthesia with fentanyl and etomidate. Fentanyl bolus injection, and particularly the additional etomidate bolus injection, produced a notable change in skin impedance over the whole clinical course. Skin impedances measured with the ESG showed a significant correlation with the bispectral index values at individual measurement time points. Many nonanesthetic factors affecting the EEG [13]. Interpretation of the raw EEG is dependent on the experience of the electroencephalographer. But with an EEG sedative effects of different agents can be monitored [14, 15].

For this study to also assess the effect produced by fentanyl and etomidate, EEGs were administered using BIS monitoring in addition to the skin impedance measurements. Although detailed information regarding the computation algorithms used [16] are still to be provided by the manufacturer, bispectral EEG analysis is deemed to be the most established EEG procedure for predicting anaesthetic depth [17, 18].

Many studies were able to demonstrate that the BIS offers a reliable measure of sedation during general

anaesthesia [19, 20]. The weak points of this method lie in the fundamental difficulty the EEG has in recording the subcortical activities during general anaesthesia. During a sevofluran anaesthesia, Katoh and colleagues found an insufficient prediction reliability of several EEG parameters with respect to patients movements in response to skin incision [21]. Another point is that also the effects of nitrous oxide, ketamine and opiates cannot be computed with the help of the BIS during general anaesthesia [22]. In a multicenter study involving 304 patients, Sebel and colleagues found that the BIS provides an insufficient prediction reliability regarding patients movements in response to skin incision in opiate-supplemented anaesthesias [23].

Fentanyl reacts on  $\mu_1$ ,  $\mu_2$ ,  $\delta$ , as well as on  $\kappa$  receptors. Agonization of the  $\kappa$ -receptor results in slight sedation. The cortex has a great abundance of  $\kappa$ -receptors which may reduce electrical activity in the cortex and thus influence the EEG values measured.

The fact that our study found an impact on BIS values after injection of fentanyl can therefore be explained by a fentanyl agonization of the  $\kappa$ -receptor, but not by an agonization of the receptors  $\mu_1$ ,  $\mu_2$ ,  $\delta$  that are responsible for analgesia [24].  $\mu$  receptors are located in the substantia gelatinosa of the spinal cord, and supraspinal locations include brainstem and sub-cortex [25].

The difference between our study and other studies addressing skin conductance measurements [26, 27, 28, 29] is that we have evaluated the effects upon the impedance of the skin of a bolus dose of fentanyl, given without additional hypnotics. Furthermore, we studied the effects generated by an additional bolus administration of hypnotics to the same patients. Impedance electrodermal response and skin conductance reflect the activity in the skin sympathetic fibers. However, the experimental settings are different. Skin sympathetic reaction is triggered in subcortical and cortical regions of the CNS with input arising from the hypothalamus, the limbic system and the basal ganglia [30]. Sympathetic efferent pathways descending from the hypothalamus run through the brainstem, synapsing with pre-ganglionic neurons in the Nc. intermediolaterales of the lateral horn. The second synapse is in the sympathetic trunk. The post-ganglionic neurites take their path as sympathetic-sudomotor fibers, together with the remaining portions of the peripheral nerves, up to neuroglandular junctions. Sympathetic activation by cortical and subcortical areas [31, 32] will therefore result in changes in the target organ, the eccrine sweat glands, that are exclusively innervated by the sympathetic nervous system. There is a direct correlation between the activity of the eccrine sweat glands and the changes in skin resistance [33]. Using the constant current technique, Lidberg and Wallin have proved that there is a direct correlation between the discharge rate of skin sympathetic nerve portions and the amplitude of the simultaneously recorded skin impedance responses [34, 35].

The involvement of cortical structures has certainly interfered with skin impedance measurements under the influence of fentanyl. It is a commonly known fact that also emotions have an influence on the values

obtained from skin impedance measurements, in addition to manual, visual and acoustic stimuli [36, 37, 38]. It can therefore be assumed that, depending on the vigilance level [39], emotions, anxieties and acoustic disturbances encountered during induction of anaesthesia for a risk-bearing cardiosurgical intervention counteracted the sedative and vigilance-reducing effect of opiate drugs [40]. The effect of fentanyl upon skin impedance probably would have been even more evident without these cortical influences. An interaction with opiate-induced effects such as nausea, thoracic rigidity, and influence on thermoregulation [41] cannot be excluded. In an intraoperative study involving 11 patients, Storm and colleagues have postulated that the analgesic effect of a general anaesthesia can be determined through measurements of the skin conductance [42]. Geddes and colleagues examined 45 patients preoperatively and found a decrease in skin conductance only after premedication with diazepam, but not after premedication with intramuscular morphine.

In our study we were able to demonstrate that fentanyl has a significant impact on the skin impedance in the absence of additional hypnotics.

The fact that there are great variances in the baseline values of the individual patients poses a problem for the interpretation of skin impedance measurement data; our own data revealed that there were patients whose skin impedance was up to ten times higher than that of others. Skin resistance is also influenced by factors such as skin condition, the measurement electrodes used, and the recording site. This causes the measurement values to spread across a wide range.

### CONCLUSION

Both administration of etomidate and of fentanyl result in direct changes in skin impedance. It appears to be possible to use the ESG for online recording of effects of opiates in general anaesthesia. Using multimodal neuromonitoring setups involving skin impedance measurements and BIS monitoring in order to predict analgesic response and depth of hypnosis (BIS) during general anaesthesia seems to be an option for the future.

*Conflict of interest:* There exists no conflict of interests.

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