In: Antibiotic Therapy: New Developments ISBN: 978-1-62808-170-1
Editors: Allen Turner and James Hall

Chapter 1

Analgesia and Sedation in Severe Sepsis and Septic Shock: A Comparison of Fentanyl/Midazolam vs. Sufentanil/Midazolam

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Abstract

Background: Pharmaceutical agents for analgesia/sedation are today mostly used in combination. In this, Sufentanil (S) should have some advantages comparatively to fentanyl (F) and is increasingly preferred in several countries, so e.g. in Germany but not in the U.S. Otherwise is not commonly proved whether the better pharmacological properties are relevant in practice. Therefore and because the complex profile of specific effects is only known in part, we evaluated data of our conversion phase from F to S.

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Methods: On each agent 7 men and 5 women in the age of 50 until 85 years with severe bacterial infection (severe sepsis or septic shock) were investigated retrospectively. All patients were ventilated by BIPAP or SIMV modus. For analgesia one group received F and the other one received S. The sedation was performed by midazolam (M) only. For comparison F vs. S at the time of maximal dosage e.g. arterial O_2 partial pressure (pO_2), arterial O_2 saturation (SO_2), mean blood pressure, heart rate, body temperature (BT), serum glucose concentration and parameters of heart rate variability (HRV) were evaluated. By performing a correlation analysis we would get information on possibly different regulatory mechanisms.

Results: Both groups were comparable (e.g. severity of illness, respiration, volume substitution, catecholamines). Only the dosage of M was higher in F ($p=0.008$) and the insulin application was higher in S ($p=0.001$) because of higher serum glucose levels ($p=0.01$). In both subgroups (F and S) similar depth of sedation on Ramsay Sedation Scale was ascertained. However, S patients received greater analgesic equivalent doses (S>5F: $p<0.001$). In maximal AS (after 6-72 hs) under S significantly higher values were found: pO_2 (after adjustment of FiO_2 and respiration frequency $p=0.015$), SO_2 ($p=0.005$), mean blood pressure ($p=0.006$), heart rate ($p=0.046$), BT ($p=0.015$), serum glucose ($p=0.01$), lnVLF Power ($p=0.006$), LF/HF ratio (0.014). The performed analysis of correlation was in accordance to a more preserved autonomic regulation under S. Under F only a correlation could be shown between some physiological parameters. Accordingly to a more prevailed anaerobic metabolism in F serum glucose correlated with serum lactate ($p=0.005$) whereas in S serum lactate correlated with arterial blood pH ($p=0.004$). Mortality under AS or until $\leq$2 days after end of infusion amounts to 6/12 in F and to 1/12 in S ($p=0.025$).

Conclusion: Considering the greater centrally induced muscle rigidity under F the oxygenation was poorer performed than under S. Also the centrally sympathetic induced influences on heart rate and blood pressure should be better preserved by S. Apart from the different autonomic regulation, already the anaerobic situation of metabolism as well as the more pronounced blood pressure decrease may thoroughly explain a greater direct mortality in septic patients when F is used. However, this must be confirmed with greater patient size.

Keywords: Analgesia, sedation, fentanyl, sufentanil, sepsis, heart rate variability

Background

Critical care patients are usually suffering from pain and other physical unpleasantness that are caused by the illness itself or by different ICU procedures. Such stressors will aggravate worse outcome if they were not diminished [1-4]. Therefore, the combination of analgesia and sedation (AS) is an essential element of intensive care today when patients must be mechanical ventilated. Whereas sooner a deep sedation until narcosis was aspired, modern therapy regimes shall secure the exemption from stress and pain, however, the responsiveness and the cooperation of the patient should be a far as possible preserved [5,6]. By so shortening the weaning-phase, the ICU stay and the complication rate can be reduced [7,8]. Accordingly, relevant drugs will be given by increasing the dose upon the wanted sedation level that can be ascertained, for example, by the Ramsay Score / Ramsay Sedation Scale (RSS). The so-called titration [6, 7, 9] will be done because measurement of plasma concentration does not produce reliable results [10].

For analgesia in Europa often fentanyl (F) or sufentanil (S) is used [11]. Both substances are fat soluble and therefore have a rapid onset of action. However, in optimizing the therapy it has become evident that S has some advantages in comparison to the older F. As such, S can be better steered because of lower accumulation [12, 13], depression of respiration is less expressed [14], and the recovery time is shorter after finishing the infusion [15,16]. In this concern not only different distribution effects are important but also the effects by the different affinity to opiod receptors. Beyond the main classification in the typs μ, κ, and δ, in μ additionally two subtypes were identified: The μ_1 receptors mediate analgesia whereas the μ_2 receptors are responsible for respiratory depression, nausea, vomiting, constipation, and euphoria [17]. Although no specific agent is available today that binds only to the μ_1 receptor, sufentanil is assumed to have more μ_1/μ_2 affinity than fentanyl [9, 18]. Thus, nausea and vomiting under S were found in minor extent [19, 20].

Furthermore, S expresses a stronger component in the δ-band of the EEG; so the use of sedatives/hypnotics can be at least reduced [20-22]. However, these pharmacological and also clinical advantages are opposed by higher preparation costs of S when only analgesic drugs were calculated [23]. Therefore, in German teaching hospitals more S and in German general hospitals more F was preferred for AS until 2005 [5]. Afterwards the use of F decreased further and then overall [24, 25]. Whereas now in Germany can be assumed that more than 50% of analgesia in ventilated patients will be

performed with S [25, 26], this is not so in the international comparison. Worldwide the more fixed combination of F/midazolam (M) [27] is always of greater relevance in such patients [28-30].

So, S is registered in the United States by the FDA as well [31], but for long-term analgesia mainly morphine or fentanyl is used; and long-term sedation is mainly performed with lorazepam or M [32]. This conception holds also true for Canada [33]. However remarkably, the role of sufentanil is only a little [32, 34]. As such, also short-acting fentanyl derivates like remifentanil are mentioned for North America either entirely not [35] or, although increasing, only marginally [36, 37]. So, there are differences in drugs and procedures; therefore, German and U.S. guidelines on AS cannot mutually transfered [5]. In consequence we must consider the discrepance that the long-term AS in the U.S. is still usually done with the combination F/M as a widespread standard method [32,38] and, by contrast, the same method will be more and more estimated to be nearly obsolete in Germany [8,26]. However, it is not structurally proved by comparison until now, whether the ascertained advantages of S vs. F are really clinically relevant. Comparative trials of fentanyl vs. sufentanil, to our knowledge, have not been performed in critically ill patients. Only more or less solitary reports are published.

But the selection of the opioid depends on its pharmacology and its potential for adverse effects. Of greatest concern are influences on respiratory, on hemodynamic, on central nervous system, and on gastrointestinal function [35]. On principle, all fentanyl derivates can lead to deep sedation (until unconsciousness), to respiratory depression (until breathlessness), to central-vagally induced bradycardia (until asystole), to severe blood pressure decrease as well as to muscle or thorax rigidity that is limiting the respiration [39-41]. Otherwise is published, that both F and S by the guidelines of the Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI) are associated with very good cardiovascular stability [5, 42]. However, Kroll and List noted a development of hypotension in critically ill and ventilated patients, especially if hypovolemia or dehydration is predisposing [43].

For getting more information in this concern we already conducted two retrospective pilot studies of the conversion from F to S. On this data revealed in a mixed patient collection (n=40) we got hints that subjects with an apriori probability to die of at least 50 % (Mortality Probability Model (MPM) II_0 [44] ≥ 0.5; $n_F=12$, $n_S=15$) should perhaps have a greater risk to die if F and not S is used in the AS (lower mortality under S or ≤ 2 days after end of infusion, respectively: 20 vs. 66.7 %; p=0.011; lower in-hospital mortality when S was used: 33 vs. 75 %, p=0.031) [45]. Secondly, we found in 2x10 mixed patients

by using heart rate variability (HRV) analysis, (1) that the reduction of autonomic regulation is clear dose-dependent in both agents and (2) that the LF/HF ratio as a marker of sympathetic predominance will be more reduced by F than by S (in lower until middle dosages: $p<0,05$) [46]. In this concern a series of publications exists that reported about prognostically unfavorable vagal predominance (LF/HF <1) [47-49]. Likewise, a more parasympathetic influenced, but overall extremely diminished HRV correlated with the severity of brain injury [50, 51].

Because these prior studies (1) depended only on a small patient size and (2) the patient size cannot be elevated easily, if a widely homogeny but severe ill population should be analyzed, we decided us for a further clinical investigation in that only patients with sepsis or severe pneumonia (SIRS criteria ≥2) were intensively researched. We investigated even such patients because this figure of disease is typical for our ICU and therefore data were completely available. Furthermore, sepsis in general is always leading to high mortality that is at the level of myocardial infarction [52, 53]. Furthermore is notable that almost one in five Americans dies in an ICU or shortly afterwards [54]. By this importance, we searched not only for pure outcome results. Moreover, we determined first outcome relevant clinical parameters (blood pressure, heart rate, oxygenation, serum glucose, serum lactate, blood pH, BT, and HRV) and then we opposed the data depending on the used analgetic agent. Further, we conducted a correlation analysis. On this we hoped to get more knowledge that can explain the found differences on the ground of already suggested regulatory mechanisms [55-58].

Methods

Design of the Study

The study focussed on the different use of the opiods F and S. Therefore we looked retrospectively for comparative patients that received either only F or only S. This precondition was especially given in the period of time when (1) F was used at the end and (2) S was used first. By this time near conception it could be widely secured that the structural premises did not change (instruments, staff, case-mix, use of other drugs etc.). Of course, so experiences were on principle better in the endphase of F than in the initial phase of S. But this aspect, as will shown in the following description, was of no relevance.

Because of the usually treated population in our ICU, even patients with severe bacterial infection are offering themselves: All such patients are severe ill and all need strong analgetics like F or S. As such, patients of a medical ICU were investigated, when they were treated because of sepsis or severe pneumonia (SIRS criteria ≥2). Recruitation was performed around the change of analgesics im the frame of AS. One group received only F for long-term analgesia and the other only S. Further only patients were enrolled in the study that received M as sedative component without exept. So the comparison F vs. S was possible. On ethics there arose no restricting questions because the change of use was fundamentally decided by information from the literature [12-16,59,60] and the now conducted study has only retrospective character. On principle, both F and S were allowed [5].

Diagnosis and Therapy

The diagnosis "bacterial infection" was obtained by clinical and laboratory chemical markers. Otherwise, blood cultures were taken; however, respective results could not be received in the acute stage of infection. So, the severity grade of infection, like "severe sepsis" or septic shock", could only be categorized by the recommended diagnosis criteria [61].

The required volume replacement therapy was mainly performed by cristalloide solutions with regard to published recommendations [62]. Catecholamines were applied in dependence of the individual state, of the need by the state and of the response of application; in most cases norepinephrine was the leading agent. This is also in accordance to general orders [61]. As hemodynamic figures should be achieved (1) a central venous pressure (CVP) of 8-12 mmHg, (2) a mean blood pressure of >65 mmHg as well as (3) a diuresis of >0.5 ml/kg body weight/hour [63, 64].

Likewise an antimicrobial therapy was conducted in adequate dosage [65] and, furthermore, by monitoring the C-reactive protein (CRP) [66,67]. As antibiotic agents mainly cephalosporines (ceftriaxone, ceftazidime), fluoroquinolones (ciprofloxacin, levofloxacin), macrolides (erythromycin, clarithromycin), imipenem/cilastatin, vancomycin, gentamycin, and metronidazole were used and as antimycotic agent fluconazole. In the case that the initial conducted therapy could not be supposed to be ultimately effective (re-increase of the CRP), the antibiotic regime was changed to other agents.

Because prognosis of sepsis is also dependent from age [68,69], we restricted our evaluation on patients with an age between 50-85 years.

Fortunately, all patients were usually either ventilated by biphasic-positive-airway-pressure (BIPAP) or by synchronized-intermittent-mandatory-ventilation (SIMV) mode (≥48 h) using the ventilator system Evita® 4 edition, Dräger AG Lübeck, Germany.

Recruitation of Patients

So, according to the intention of the study following inclusion criteria and exclusion criteria were formulated:

Inclusion criteria:

1. Severe bacterial infection treated in the ICUSchwere (SIRS criteria ≥2 [61]),
2. F or S for analgesia,
3. M for sedation,
4. 50-85 years,
5. AS expected to require ≥72 hours.

Exclusion criteria:

1. Other drugs for AS (including central α-agonists and butyro-phenones),
2. neuromuscular blocking agents or antidotes,
3. another indication that would already lead to ICU admission (e.g. myocardial infarction, stroke, intoxication, respiratory failure, hypertensive crisis, anaphylactic shock),
4. a chronic disease that would relevantly compromise the autonomic nervous system (e.g. diabetes mellitus, terminal renal insuffiency, liver cirrhosis Child C, Guillain Barré syndrome).

On these restricting criteria we were able to find 2x12 septic patients (7 males und 5 females, respectively). The patients that received F originated from the endphase of the application. Currently, for comparison the next patients receiving S were examined. All patients that fulfilled the preconditions mentioned above took part in the investigation. The sedation if necessary was performed by M in all cases. A co-medication with propofol, ketamine and/or clonidine led to exclusion and the administration of naloxon or flumazinil as well.

From the rule in general, that either only F/M or only S/M must be used, single bolus applications initially before intubation were exempted. The intubation in both agents (F and S) was mainly performed under a combination of etomidate, F and M (10x before continuous F infusion; 8x before continuous S infusion). In 3 times the intubation took place simultaneously to reanimation procedures, in 2 times was already externally performed by the emergency physician, and in 1 time was done before a surgical procedure.

Accordingly, in critically ill patients with sepsis etomidate is widely used as an inductive hypnotic for intubation because of its hemodynamic safety, fast onset, and short duration of action [70, 71]. However, there are studies that gave hints for greater mortality in sepsis because of adrenal insufficiency [72] whereas in other investigations no increase of mortality by a single dose of etomidate was found [73, 74]. Nevertheless, the use of etomidate is controversly discussed [75, 76].

Analgesia and Sedation

From interrogations of post-ICU patients we know that physicians as well as nurses are typically estimatating the need of analgetics as too low [77,78]. So, approximately 75% of ICU patients reported severe pain during their treatment, however, more than 80% of the care givers considered the analgesia to be adequate [79]. Thus, adequate monitoring of analgesia is relevant for outcome of critically ill patients that are widly unable to communicate [80]. Unfortunately, the requirement of analgetics and sedatives differs from patient to patient.

Upon these difficulties we tried to reach an individually adapted state that screened the respective patient as well as possible. As such, we looked in first line to analgesia as much as possible but in accordance to acceptable blood pressure and respiration, and in second line to sedation in accordance to non-agitation. In this purpose the perfusors of 50 mL were filled with either 0.5 mg F, 0.75 mg S or 200 mg M. The then applicated dosages oriented first to own experience data or to instructions from the literature; however, such are not always consistent. In finding the adequate dose we orientated us to figures from the literature, as there are 30-100 µg/h in F [81], to 10-50 µg/h in S [5], and to 10-20 mg/h in M [82], when patients with normal body weight are concerned (ca. 70 kg). Boluses were not given because patients were mostly simultaneously intubated and therefore treated with a combination of etomidate, fentanyl and midazolam. Basically to this, AS began with low

dosage first in opioids, but also doses of M were elevated continuously (= titrated) to wanted level of analgesia and sedation [6,7]. This retarded proceeding was performed for minimizing the risk of blood pressure decrease and bradycardia that may occur by too rapid infusions [83,84], and for reducing the respiratory depressant effects caused by a so likewise increased thorax rigidity as well [10,39].

Therefore, it was the aim as should aspired before [8, 85] (1) to perform the best possible analgesia in that (2) the patient was still hemodynamically and respiratory stable. Furthermore, (3) the patient should be good sedated and only less distressed. Otherwise, (4) overdoses in analgesia and sedation should be also avoided [8, 86]. As such, the right doses should be found by using modern scoring systems [5, 35]. However, patients with sepsis are often only restricted able to communicate [87]. Thus, the in general recommended evaluation of analgesia and sedation by such systems is limited when patients are not able zo be cooperative; instead of then subjective parameters must be used for compensation [35]. In the sense of the Behavioral Pain Scale (BPS) which was developed for uncommunicative patients [88], we looked for counter regulations in finding the adequate doses like movement, facial expression, and physiological parameters. Changes in blood pressure, agitation, sweating, lacrimation, dysyncronous respiration etc. could be interpreted as a sign of a stressig situation on the ground of an inadequate AS [89]. As such, first line interest was analgesia that was simultaneously augmented by M.

By the difficulties on principle, in the researched patients it was tried to reach a sedation grade of maximal 3 upon the RSS [90, 91], as far as possible, by dosage of F/M or S/M, respectively [92]. However, the recommended target of 2-3 that would enable the patient to cooperate [5,6] was often exeeded in both groups (F and S), because most patients were already central nervously impaired due to their septic illness and were therefore somnolent until comatose already without AS [87]. Accordingly to such difficulties the not always clear-cut discrimination that is mentioned for the RSS [93] was of subordinated importance. In this study only the attained sedation grade should be group related compared (F vs. S).

Proof of Equality and Measurement of Impairment

With respect to equality of F and S use it was examined whether both groups were comparable in severity of illness upon the Mortality Probability

Model (MPM) II_0 [44,94], SIRS criteria, the maximum of CRP, body weight, and the source of infection. Accordingly to the MPM II already new versions exist but the older ones also recently still have shown acceptable reliable results in discrimination and calibration [95].

Under the preconditions as described above wie evaluated the data on (1) respiration and oxygenation, (2) heart rate and its variability, (3) BT, (4) energy supply and (5) outcome. The physiological parameters were either hourly measured (blood pressure, heart rate, oxygen supply, oxygen saturation, heart rate variability) or every 4-6 hours in relation to the acute critical state of the patient (blood gas analysis and CVP). For blood gas analysis the analyzer system AVL Omni® 9, Roche Diagnostics, Graz, Austria was used.

The so received results first were agent specific opposed. Afterwards correlation analyses were performed. In this, documented data from the clinical history were used. By the additionally conducted HRV analysis we would get more differentiating information that is overtopping the pure net effects like blood pressure and heart rate. So, new coherences with such parameters should be detected from that is known that they are responsible for positive or negative outcome.

Assessment of HRV Parameters

HRV tests are non-invasive objective tools for quantifying the changes in cardiac autonomic nervous system. All figures are decreased if autonomic functions are impaired. For getting information we used the continuous online system Cardiovision® MTM multitechmed, Huenfelden, Germany. For such determination, first the QRS complexes (lead II) were automatically recognized by classic methods. Then all irregular heartbeats and artefacts were removed and the resulting missing data were replaced by linear interpolation with the the three preceeding and the three succeeding complexes. Limitary, electrocardiac tracings with >1% premature beats would be eliminated from the analysis. The so received analog signals were next converted to digital with a sampling rate of 256 Hz and a 12 bits amplitude resolution.

On the digitized and hourly related data, then parameters for both time domain and frequency domain measurements were analyzed according to the guidelines of Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [96]. By using time-domain analysis the standard deviation of normal interbeat intervals (SDNN) as a global marker and the square root of the mean of the sum of squared

differences of successive interbeat intervals (rMSSD) as a marker of vagus nerve activity were calculated. The power spectral density was calculated by using a Fast Fourier Transformation. The so revealed measures in the frequency-domain divided the Total Power (TP; 0.003-0.4 Hz) into Very Low Frequency Power (VLF; 0.003-0.04 Hz), Low Frequency Power (LF; 0.04-0.15 Hz) and High Frequency Power (HF; 0.15-0.4 Hz) as is published by the already mentioned Task Force guidelines [96].

Accordingly, the HF component correlates with parasympathetic activity and the LF component correlates both with sympathetic and parasympathetic activity. Therefore the LF/HF ratio should be a marker of sympathetic vagal balance. High values of LF/HF-Ratio are a marker of sympathetic predominance, and low values, therefore, a marker of a vagal predominance. Not so clear is the role of VLF. Until now is hypnotized that VLF is associated with thermoregulatory function [97] and with sympathetic contribution to vascular regulation as well [98]. But also the interplay of different organs in relation to the HRV is supposed [56]. As such, especially the VLF band in relation to sepsis and multiple organ dysfunction syndrome (MODS) should be very important [99]. Because especially the parameters of frequency domain are not linearily ruled by increasing influences [100] usually a natural log-transformation (ln) will be performed prior to statistical analysis [99-102]. Such right-skewedness is often not described for the LF/HF ratio and for time domain parameters in already impaired patients with lower HRV figures [100,102], but by contrast also, for example, when healthy young males with higher HRV figures are concerned [103].

Minimal HRV for Definition as Most Critical Measuring Point

The investigation focussed upon the first and acute phase of severe bacterial infection. In that period of time it can be assumed already by the course of CRP (CRP maximum) that the patients were mostly impaired and therefore at highest risks [66, 67]. Simultaneously, the need of agents for AS was maximal already because of mechanical ventilation, other discomfort and prolonged immobilization as well. So it follows that the parameters of HRV and therefore the autonomic functions were found maximal diminished. And this early critical state of the patient (6-72 hours after ICU admission) gave not really a reason to think about the usually recommended sedation interruptions [6, 26]. The primary demands of the patient as well as the main tasks on

physicians or nurses were much different from later weaning and recovery phases [104].

Thus, because the basic state of autonomic nervous system before the criticall illness was unknown as such as the course of illness can be individually much different, we chose for our investigation even that fixing point when HRV was presenting the lowest figures (6-72 hours after ICU admission and after beginning of mechanical ventilation). At that time AS was given at highest dosage already for some hours and therefore a steady state can be assumed. However, we must more than suggest that the illness in septic concern had become much worse parallel to elevation of dosage for AS until response of antimicrobial treatment would have led to clinical improvement. Additional effects must be supposed (for example multiple organ dysfunction [99], CRP [105], volume substitution [106] and perhaps also different antibiotics [107]). With respect to such influences it was to prove that those parameters were either comparable or were unseparably connected with the use of F or S.

Because the highest CRP value was nearly found to the defined measuring point (HRV minimum) and afterwards CRPs as well as doses in AS decreased, it can be thoroughly supposed that the period with maximal HRV depression is much critical for the patient, and, certainly, is announcing the time in that the patient is most endangered overall [57,58,99]. Acccordingly to this inquiry the course of parameters in detail over time is not primary important; much more relevant for outcome it should be, what state of minimal autonomic function must be run through or, much more, must be endured by the patient [105,106,108,109]. In this concern we could already find that the HRV in doxepin intoxication reached minimal values on average after 5.4 hours according to ICU admission [110]. Remarkably, the greatest mortality rate in intoxications with tricyclic antdepressants without specification in another investigation was also seen on average after 5.4 hours after ICU admission [111].

Statistical Analysis

All continuous data that were analyzed by IBM®SPSS® statistics version 21.0 (Somers NY; USA) are expressed as mean ± standard deviation. Categorical data given in frequencies were compared with the χ^2-test. The Kolmogorov-Smirnov-test was performed for detecting, whether the figures are normal distributed or not. The comparison of parameters between the

groups was performed by using the student-t-test for parametric conditions and by using the Mann-Whiteney-U-test for nonparametric conditions. Because of skewed distribution in HRV parameters (exept LF/HF) a natural logarithmic transformation was performed before statistical analysis [99-102]. So, statistics are possible on parametric level. The association between the parameters was carried out by Pearson´s correlation (Pearson´s rho; r_P) or by Spearman´s correlation (Spearman´s rho; r_S), respectively. A p-value <0.05 was considered to be statistically significant. Additionally, we mentioned the borderline non-significance until p=0.1.

Results

The first part of the Table demonstrates that both groups (F and S analgesia) were comparable from the basic data. Similar held true for the examined depth of sedation according to the RSS (3.9 ± 1 vs. 3.8 ± 0.7). However, for achieving of adequate AS higher doses of M were used when F was applied (p=0.008 after adjustment to body weight). Because patients of both groups were only less different ventilated either by biphasic-positive-airway-pressure-ventilation (BIPAP) or by synchronized-intermittent-mandatory-ventilation (SIMV), this cannot reflected to specifics upon the ventilation mode [112]. Much more as it was already mentioned above [20-22], this must be expected [9,113].

Furthermore, under S were significantly higher equivalent doses administered (p<0.001) because S in comparison to F is more than 5 times more analgetically effective [22,114], Also is to remark that a greater dose of insulin was necessary under S than under F (p=0.001) because of also higher serum glucose levels (p=0.01). These differences, especially the greater analgesia in the use of S, must beconsidered in the valuation. Otherwise, the groups were comparable, and this also in reaching the point of maximal HRV depression (6-72 hrs after ICU admission).

Table. Synopsis of the results a) basic data und data upon AS, b) differentiating figures on therapy (F vs. S)

	Fentanyl (F)	**Sufentanil (S)**	p
Basic data			
N	12	12	
Male/female	7/5	7/5	

Table. (Continued)

		Fentanyl (F)	**Sufentanil (S)**	p
Basic data				
Age [years]		69.7 ± 11.6	68.8 ± 9	n. s.
Body weight [kg]		74.8 ± 11.6	76.9 ± 10.1	n. s.
MPM 0 [%]		64.4 ± 14.9	63.8 ± 18.3	n. s.
Sepsis		67 %	67 %	n. s.
Severe pneumonia		33 %	33 %	
SIRS criteria		3.5 ± 0.7	3.7 ± 0.5	n. s.
CRP maximum [mmol/L]		226 ± 95	234 ± 99	n. s.
Severe sepsis (≥ 1 organ failure)		25 %	25 %	n. s.
Septic shock		75 %	75 %	
HRV minimum after intubation in hs		33.3 ± 22.2	28.9 ± 21.3	n. s.
Depth of analgesia/sedation (AS)				
Maximal **F** or **S** dosage [µg/kg/h]		0.723 ± 0.307	0.496 ± 0.263	0.065
Analgesia equivalence (**S** > 5 x **F**)			> 2.479 ± 1315	<0.001
Midazolam [mg/kg/h]		0.428 ± 0.158	0.261 ± 0.12	0.008
Ramsay Sedation Scale (RSS)		3.9 ± 1	3.8 ± 0,7	n. s.
Ventilation und oxygenation				
Mode of ventilation	BIPAP	58 %	67 %	n. s.
	SIMV	42 %	33 %	
Ventilation frequency [/min]		11.6 ± 2.2	11.2 ± 2	n. s.
FiO_2 [%]		42.9 ± 13.7	41.3 ± 12.3	n. s.
pO_2 [mmHg] arterial		75 ± 11.8	111.7±28.8	<0.001
pCO_2 [mmHg] arterial		41.6 ±8.8	42.7 ± 6.8	n. s.
pO_2/ventilation frequency		6.7 ± 2	10.3 ± 3.3	0.005
pO_2/FiO_2 (Horowitz quotient/100)		2 ± 0.9	3 ± 1.1	0.023
pO_2/ventilation frequency x pO_2/FiO_2		14.4 ± 11.7	32.3 ± 20.4	0.015
SO_2 arterial [%]		94.3 ± 1.6	96.5 ± 1.9	0.005
Correlation (r_p) pO_2/ventilation frequency vs. LF/HF		0.131	0.597	n. s. / 0.04
Correlation (r_p) pO_2/FiO_2 vs. VLF (ln)		0.092	0.705	n. s. / 0.01
Correlation (r_p) SO_2 arterial vs. Total Power (ln)		0.067	0.666	n. s. / 0.018
Correlation (r_p) SO_2 arterial vs. VLF (ln)		0.354	0.626	n. s. / 0.03
Correlation (r_S) pCO_2 vs. pO_2		0.615	-0.293	0.033 / n. s.
		Fentanyl (F)	**Sufentanil (S)**	p
Blood pressure and circulation				
Dopamine and/or dobutamine		33 %	33 %	n. s.
Norepinephrine and/or epinephrine < 2mg/h		33 %	42 %	
Norepinephrine and/or epinephrine ≥ 2mg/h		33 %	25 %	
pH arterial		7.33 ± 0.08	7.33 ± 0.06	n. s.

	Fentanyl (F)	**Sufentanil (S)**	p
Blood pressure and circulation			
Volume substitution [mL/h]	104 ± 43	101 ± 34	n. s.
Systolic blood pressure [mmHg]	101 ± 9	112 ± 10	0.012
Diastolic blood pressure [mmHg]	46 ± 6	54 ± 9	0.019
Mean blood pressure [mmHg]	64 ± 6	74 ± 9	0.006
Central venous pressure (CVP) [mmHg]	6.8 ± 1.6	8.6 ± 1.6	0.015
Correlation (r_p) systolic blood pressure vs. VLF (ln)	-0.211	0.736	n. s. / 0.006
Correlation (r_p) diastolic blood pressure vs. VLF (ln)	-0.174	0.424	>0.5 / >0.1
	Fentanyl (F)	**Sufentanil (S)**	p
Blood pressure and circulation			
Correlation (r_p) mean blood pressure vs. VLF (ln)	0.473	0.597	n. s. / 0.041
Correlation (r_P) systolic blood pressure vs. pO_2	-0.131	0.14	n. s.
Correlation (r_P) systolic blood pressure vs. serum glucose	0.292	-0.304	n. s.
Heart rate and heart rate variability			
Heart rate [/min]	93 ± 21	109 ± 18	0,046
Total Power (TP) [/sec^2]	10.9 ± 9.8	15.2 ± 13.5	>0.1 (ln)
VLF [/sec^2]	1.6 ± 1.4	5.7 ± 5	0.006 (ln)
LF [/sec^2]	0.9 ± 1.3	1.5 ± 2.4	>0.1 (ln)
HF [/sec^2]	6.8 ± 6.1	6.4 ± 9.2	>0.5 (ln)
LF/HF	0.15 ± 0.07	0.25 ± 0.12	0.014
SDNN [/sec]	7.2 ± 2.4	8.6 ± 2.7	>0.1
rMSSD [/sec]	8.3 ± 2.6	7.9 ± 2.2	>0.5
Correlation (r_p) Heart rate vs. TP (ln)	-0.694	-0.631	0.012/ 0.028
	-0.458		0.024
Correlation (r_p) Heart rate vs. HF (ln)	-0.746	-0.751	0.005/ 0.005
	-0.675		<0.001
Correlation (r_p) Heart rate vs. SDNN	-0.658	-0.709	0.02 / 0.01
	-0.517		0.01
Correlation (r_p) Heart rate vs. rMSSD	-0,694	-0,749	0.012/ 0.005
	-0.655		0.001
Correlation (r_p) Heart rate vs. pO_2	0.379	0.082	>0.1 / >0.5
	Fentanyl (F)	**Sufentanil (S)**	**p**
Body temperature			
Body temperature (BT) [°C]	36.9 ± 0.6	37.7 ± 0.9	0.015
Correlation (r_p) BT vs. pO_2	0.274	-0.028	>0.1 / >0.5
Correlation (r_p) BT vs. TP (ln)	0.328	-0.57	n. s. / 0,053
Correlation (r_p) BT vs. VLF (ln)	0.352	-0.281	n. s.
Correlation (r_p) BT vs. LF (ln)	-0.198	-0.649	n. s. / 0.022
Correlation (r_p) BT vs. HF (ln)	0.01	-0.582	n. s. / 0.047

Table. (Continued)

	Fentanyl (F)	**Sufentanil (S)**	p
Body temperature			
Correlation (r_p) BT vs. SDNN	0.545	-0.703	0.067/ 0.011
Correlation (r_p) BT vs. mean blood pressure	-0.357	-0.11	>0.1 / >0.5
Energy supply			
Glucose 50% p. inf. [mL/h]	26 ± 6	24 ± 5	n. s.
Insulin application [IE/h] pro kg	2 ± 1.8	5 ± 2.1	0.001
Serum glucose [mg/dL]	206 ± 53	291 ± 89	0.01
Serum lactate [mmol/L]	3.7 ± 3.5	4.4 ± 2.9	n. s.
Correlation (r_p) serum glucose vs. serum lactate	0,745	0,444	0,005 / n. s.
Correlation (r_p) serum lactate vs. pH arterial	-0.163	-0.767	n. s. / 0.004
Correlation (r_S) pCO_2 vs. serum glucose	-0.559	-0.375	0.059 / n. s.
Correlation (r_S) pCO_2 vs. pO_2/serum glucose	0.713	0.007	0.009 / n. s.
Correlation (rp) serum glucose vs. LF/HF	-0.112	0.758	n. s. / 0.004
Correlation (rp) serum glucose vs. VLF (ln)	0.06	-0.13	n. s.
Arrhythmia incidence und outcome			
Supraventricular extrasystoles (SVEs) in 24 hs	1492 ± 1384	1024 ± 1513	n. s.
Ventricular extrasystoles (VEs) in 24 hs	279 ± 353	240 ± 305	n. s.
β-Lactam antibiotics	7	10	n. s.
Fluoroquinolones	5	3	
Macrolides	4	4	
Aminoglycosides	4	2	
Vancomycin	6	9	
Metronidazole	5	6	
Fluconazole	7	6	
QTc-Interval prolonging drugs	11	11	
In-hospital mortality	9 (75 %)	5 (42 %)	0.1
Standardized Mortality Ratio (SMR)	1.165	0.648	
Mortality under or ≤ 2 days after infusion	6 (50 %)	1 (8 %)	0.025

In the instruction upon the ventilation no changes were seen in the conversion phase from F to S. As such, not only the mode of mechanical ventilation did not change but also the ventilation frequency as well as the inspiratory oxygen concentration (FiO_2) overall. However, the respiration

under S was more effective; the uptake of oxygen was significantly higher than under F. This could be shown by the arterial oxygen partial pressure (pO_2) even after adjustment to the ventilation frequency (p=0,005) or to the FiO_2 (Horowitz quotient; p=0.023) as well as by the arterial oxygen saturation (SO_2; p=0.005). With the better SO_2 correlated the lnTP and the lnVLF of the HRV under S (after ln transformation parametric: p=0.018 and p=0.03, respectively), but not so under F. Likewise, the pO_2 correlated with the lnVLF after adjustment to FiO_2 and with the LF/HF ratio after adjustment to the ventilation frequency, both only in the S group (r_P=0.705, p=0.01 and r_P=0.597, p=0.04, respectively).

Whereas the pO_2 under S was significantly different from the pO_2 under F ($p<0.001$) this did not hold true for the partial pressure of CO_2 (pCO_2). This was on average also even higher under S, however, only a little bit. With respect to possible correlations the analysis revealed a positive proportional coherence of the pCO_2 and the pO_2 under F, but only on non-parametric level (r_S=0.615, p=0.033). In the S group this connexion was gradually negative.

Accordingly to blood pressure and circulation there was a stronger blood pressure decrease by F than by S (systolic > diastolic; p=0.006 in the mean pressure). Similar held true for the central venous pressure (CVP; p=0.015). However, the application of catecholamines was very variable and no specific difference between F and S could be detected. In 62.5% (7F and 8S) norepinephrine was the leading agent. This is in accordance to the guidelines in general [61]. Also the volume substitution (mainly cristalloids) was comparable. Under those conditions we found only a positive correlation (r_p) between systolic blood pressure and the lnVLF and such only under S (p=0.006).

The agent specific differences in heart rate were comparatively less expressed ($RR_S > RR_F$), but level of significance was also reached (p=0.046). Accordingly to the HRV, differences were attained especially in the VLV band after natural log-transformation (p=0.006) as well as in the sympathetic-vagal balance (LF/HF ratio; p=0.014). With respect to a correlation of heart rate and HRV no substance specifity on principle was found. With a more preserved HRV (especially of HF power and of rMSSD) the heart rate was diminished in both F and S (overall $p<0.001$ and p=0.001, respectively).

Also in BT we found differences. The values were higher under S than under F (p=0.015). In this the figures in S correlated with some HRV parameters negatively (SDNN and lnLF-Power, p=0.011 and 0.022, respectively). However, between BT and blood pressure no significant

interactions were found. Tendentiously, a low blood pressure was rather associated, remarkably, with a higher temperature.

With respect to provision of energy, by comparable application higher glucose concentrations were measured in S than in F (p=0.01), and this, although in S greater amounts of insulin were given (p=0.001). Otherwise, higher levels of lactate in S were found, but no level of significance was reached. Further it was interesting that the correlations were agent specific: Whereas the glucose and lactate levels were positive connected under F (r_P=0.745, p=0.005), under S we found a negative coherence of lactate and arterial blood pH (r_P=-0.767, p=0.004). In the concern of potential correlations and therefore interactions, the data on F showed not only a positive proportional connexion between pCO_2 und pO_2 (s.above), but also a negative proportional connexion between pCO_2 and serum glucose (r_S=-0.559, p=0.059), and in combination a rather additing influence could be ascertained (r_S=-0.713, reduction of p=0.009). This was not so under S; here we found a positive coherence of the serum glucose with the LF/HF ratio (r_P=0.758, p=0.004).

The incidence of supraventricular as well as of ventricular arrhythmias was only tendentiously higher in the F group. This is accompanied with a use in a similar extent of antibiotics/drugs that are responsible for QTc-interval prolongation and that can elevate the risk of arrhythmia occurrence [115-117]. This could be also in accordance to the result overall, that the in-hospital mortality was not significantly different (p=0.1). However, the negative outcome under AS or in the first phase after finishing the opioid infusion was different. As such, difference in mortality during AS directly and also during the following 2 days attained relevance, because a retarded effect (hangover) must be assumed at least in F [12, 13, 59, 60] (F vs. S: p=0.025).

Discussion

Achieving and maintaining the adequate levels of analgesia and sedation is essential in modern ICU care [26,37]. Therefore, understanding the clinical pharmacology of commonly used sedative agents and opioids is always necessary. Only then clinicians are able to find the best dose desired for clinical effect while minimizing the risk of excessive sedation and cardiopulmonary depression [118]. Despite of the great importance in general only few comparative and controlled studies were performed in this field.

Mostly reports from experience and more or less singular descriptions are published.

Whereas formerly in Germany a standard combination of F and M was employed for AS [27], today the recommended conceptions are more complicated and differentiated [8, 26, 119]. However, therefore the instructions have become more difficult to survey. Furthermore, the use of the respective agents is much different in the international comparison [5,11], and worldwide even the fixed combination of F/M has still great relevance [28,29,34,120]. These discrepancies surely have added that now the particular therapy options can be hardly judged by the diversity of diseases.

On the ground of the already known advantages of S (for example, lower accumulation, less respiration depression, shorter weaning phase) [12-16, 59,60,121] one cannot wonder that F in Germany was more and more replaced by S already on pragmatic consideration [24-26]. Already the published data gave surely good arguments for changing to S despite higher direct medicament costs [23]. However, in this replacement no examination of hard facts on the therapeutic success was peformed. A detailed documentation of clinical relevance is missing. Likewise, the opportunity for better knowing the specific pharmacodynamic profile was omitted. Now, afterwards the performance of prospective controlled trials is problematic, for example, in Germany because it must be supposed thoroughly that S has several relevant advantages comparably to F.

Appropriateness of Analgesia and Sedation

Unrelieved and distressing symptoms are present in the majority of intensive care patients. As such, especially mechanically ventilated patients experience pain in different degree that may lead to agitation. However, not only the discomfort by the endotracheal tube is relevant but also the placement of invasive catheters, the endotracheal suctioning and the situation of immobility must be taken into account. All these factors represent stressors if were not diminished they may significantly worsen patients´ outcome [122]. Herein, the incidence and intensity of pain in medical ICU patients are not lower than in surgical and trauma ICU patients [123].

For avoiding or at least minimizing unnecessary suffering such patients frequently require analgetics and sedatives [6]. However, recognition of the presence of pain and discomfort is rendered more difficult because mechanically ventilated patients with sepsis are often unable to convey and

also clinical parameters like tachycardia, blood pressure increase, unrest, sweating, lacrimation, reaction an movement or posturing, ventilator-respiration dysynchrony, facial expression etc. [89] are not reliable indicators [35]. So, pain in not-communicative patients can be either underestimated or can be misinterpreted as agitation that cannot be treated effectively with sedatives alone.

If the patient is not sufficiently screened form pain and anxiety, the as such feeled emergency situation will lead to a series of vegetative reactions like tachycardia, increased oxygen consumption, hypercoagulopathy, immune suppression and persistent catabolism [1,3]. Moreover, pain may contribute to pulmonary dysfunction by increasing muscle rigidity; so the mobility of the chest and the diaphragm will be restricted [2] that is thoroughly relevant for outcome [4]. Already from this aspect an adequate AS is essential in intensive care [85, 89,124].

However, opioids as well as benzodiazepines are very effective but also potentially toxic substances; therefore on the other hand overdoses should be avoided as far as possible. But because patients with sepsis are often not enough able to communicate the need of analgetic drugs cannot be measured sufficiently. Thus, assessment by self-rating scales is excluded on principle. Furthermore, pain associated behavior as well as physiologic parameters and their changes on analgetic treatment could not always be interpreted reliably, especially in the middle range [125]. Therefore, the estimation of pain remains as a problem. Several studies have shown that painful situations were often not realized in real extent [77-79]. For getting to the safer side we tried to apply analgetics in as much as high equivalent doses that were preserved by acceptable compatibility.

With respect to sedation a RSS level of 2 (cooperative, oriented and tranquil) - 3 (drowsy, but responsive to commands) is to aspire on modern guidelines [6,26]. By this conception it is the aim to awaken the patient once a day. However, the defined grade of sedation is specificly different und is dependent from the concerned patient population [88] as well as from the used agents [91]. As such, also a RSS of 3 - 4 (asleep, brisk response to stimulus) is published to be optimal [7,38]. Although the RSS will be criticized because of a not always clear-cut discrimination [5,93], nevertheless, the RSS is most often used in Canada [33] and in the U.S. in similar extent as the Glasgow-Coma-Scale (GCS) [32]. Accordingly to our study we found that the more recommended use of the Richmond Agitation Scale (RASS) [8, 26, 126] would have not revealed any advantages. All patients then would be assessed by -2 - -5 analogously to RSS 2 - 5.

Overall, no relevant differences between F and S were found in the reached level of sedation (RSS 2-3 was the aim, nearly 4 in mean was ascertained). By contrast the chosen doses of F and S are striking when they were compared in analgetic equivalence. The proportion S/F in application amounted in mean to ca. 2/3 (0.496 vs. 0.723 µg/kg/h) although the pain scores in the literature were already lower ascertained under S when the dose of S was 1/10 [20,127].

Under the assumption that S was more than 5 times more analgetically effective than F [60,114,128] the given doses in our investigation either must be estimated as too low in F or perhaps as too high in S ($p<0.001$).

Concerning to S, it can be stated that the chosen dosage of 7.5-90 µg/h was in accordance to the recommendations in general (for instance, until 50 µg/h [5] or until 70 µg/h in normal body weight [43]). This is in contrast to F where higher doses are much often mentioned in the guidelines (until 245 µg/h in body weight of 70 kg [5]) than we have used and have found retrospectively (10-100 µg/h). However, also lower dosages are recommended in continuous infusions (until 35 µg/h) [129]. As such, our doses were in the middle and are in accordance to elsewhere given orientations as well (30-100 µg/h) [81].

Also the question is, whether the treated critically ill patients with a MPM II_0 of more than 50 % would have really acceptable tolerated higher doses of F.

This must be queried upon the following explanations. On the other hand, reducing the S dosage cannot be seriously considered, because 50-70 % of critical patients reported about pain after ICU therapy [77-79]. By contrast 80 % physicians and nurses were the opinion that their patients were sufficiently treated on pain.

In summary we can suppose that a better analgesia can be performed by S than by F, at least in comparable level of sedation and when for sedation M is used. Furthermore, a S dosage that may be to high should be excluded; on the Standardized Mortality Ratio (SMR) of 0.648 this is not rather probable. However, the M doses for augmentation in F were indeed relatively high (recommendations until 0.18 mg/kg/h [5], description until 0.29 ± 0.20 mg/kg/h [82], use in our examination 0.43 ± 0.16 mg/kg/h in F and 0.26 ± 0.12 mg/kg/h in S; $p=0.008$).

How the Dosage of Midazolam must be Estimated in the Fentanyl Group?

Despite of several recommendations [5, 35] the dose of F seemed to be not gradable. From the clinical reaction we had to expect that the patients would have not endured a further elevation of F, either in oxygenative concern and/or hemodynamically. This is underlined by the data on HRV analysis (see below). However, by this dosage in comparison to S the patients were not equivalently treated for pain ($p<0.001$). Therefore, greater sedation with M was compensatory more necessary in F than in S (in mean factor 1.65). Such M doses in F on the one hand were higher than the recommended (in mean factor 2.4) [5], but on the other hand such figures are not unusual in septic patients and were even described in detail [130]. The higher needs should causally due to tachyphylactic alterations [131]; however, there also exist controverse results [132].

Although sedative drugs in the critically ill may contribute to severity of illness and possibly to mortality [131] it is not very probable that the 1.65 times more use of M in the F group had caused the crucial changes in autonomous nervous system. As such, midazolam is characterized by a high therapeutic index in general [132,133]. Furthermore, the vagal function was more diminished under benzodiazepines than the sympathetic [134]. Therefore, rather a reduction in absolute HF power as well as an elevation of LF/HF ratio [135] or at least no change on LF/HF ratio [136] should be expected in greater M application [137] and this should be also more accompanied by an increase of heart rate [134]. However, remarkably, especially the latter results founded on relatively low dosages (0.07 mg/kg) and are not related to critical care patients. As such, on an already much impaired autonomic function an additive negative effect on outcome because of net sympatheticolysis cannot be excluded [138,139]. So, also a mild hypotension on principle may become an additional complication factor in the critically ill. But this phenomenon was more seen during the loading dose [140,141]; during titrated continuous application critically ill patients were hemodynamically stable [133,142]. Furthermore, this aspect should be of minor relevance when M is compared with propofol [143,144].

Similar holds true for respiratory complications. Although benzodiazepines in comparison to opioids are different in mode of respiratory depression [37], nevertheless, they are impairing the oxygenation. As such, especially induction doses of M can reduce the ventilatory response to CO_2, can decrease minute ventilation, and can cause apnea [132]. Such effects by M

in comparison to F should be surely of less importance. Thus, only 3% of 207 patients in oral surgery were apnoic (spontaneous respiration frequency <1/30sec) when they received only M and, by contrast, 63% were apnoic when they received a combination of F and M [145]. However, such adverse effects cannot be ultimately separated under the given preconditions in that opioids and M should act synergistically with regard to sedation [146,147]. If opioid requirements should decrease, sedatives such as M infusions must be administered compensatory [148]. This implicates further that such side effects cannot be avoided because they are directly coupled; and the restricting consideration on the use of M is finally irrelevant for clinical practice, because the patients should as far as possible be screened sufficiently, by F/M as well as by S/M.

Ventilation und Oxygenation

A further aspect is the ultimately different expression of respiratory depression in the F and in then S group. By this, in pharmacological concern it is not only meant the pulmonary compensated increase of arterial CO_2 but also the decrease of arterial O_2 as well as the decrease of the pH. Thus, the reduction of the drive to ventilate and the impairment of ventilator mechanics are considered in summation [149]. Whereas the deficient pulmonary drive can be bridged by mechanical ventilation, impairment in gas exchange is not so easy to remove. Our results again gave hints that the blood and the organism will be worse oxygenated under F in the conception of a more induced thorax rigidity than under S ($p<0.001$) [10, 14, 59]. Even after correction on the ventilation frequency and/or on the concentration of the inhalated oxygen the difference reached level of significance ($p<0.025$). Similar held true for the arterial SO_2 ($p=0.005$). This is so far important as a progressive O_2 deficiency limits also mycardial contractility [150].

Whereas a hypoxemia under physiological conditions will be replied by an increased sympathetic activation mediated by carotic chemoreceptors [151,152], in F can be at least supposed that the counter-regulation is less expressed in comparison to S. As such, the arterial SO_2 correlated with the natural logarithm of the Total Power density in S ($r_P=0,666$, $p=0.018$), but not so in F. Likewise, the arterial pO_2 correlates only in S with two parameters of HRV: (1) with the natural log-transformed VLF band after adjustation to the FiO_2 ($r_p=0.705$, $p=0.01$), and (2) with the LF/HF ratio after adjustment to ventilation frequency ($r_P=0.597$, $p=0.04$). In comparison, also global HRV

parameters are diminished in COPD patients. Whereas sympathetico-vagal balance was not always altered in the sense of sympatheticolysis [153-155], nevertheless, the LF/HF ratio correlated positively with the arterial pO_2 in spontaneous respiration [153]. Analogeous relations we found in S, but not so in F analgesia.

The so ascertained diminution of oxygenation in F is referred to an increased expiratory muscle activity by a likewise increased abdominal pressure or abdominal muscle tonus [156]. Hereby also the end-experiratory lung volume, i.e. the functional residual capacity, is reduced [157]. Basically to that state the arterial SO_2 was reduced even by a FiO_2 >30% [158]. Thus for example, severe complications in dental procedures were ascertained relatively rare (13 cases in 15 years), but if they occurred, hypoxemia was often the reason for such events, either they could be referred to an airway obstruction and/or to a respiratory depression [159].

Upon the arterial blood gas analysis was shown that the pCO_2 in the F group was not different from the S group. Tendentiously the pCO_2 was found even to be less in F (n. s.), although the pO_2 under S was examined in much higher figures ($p<0.001$). Therefore, in reduced respiratory function under F rather a greater pCO_2 should be expected in F than in S. However, such information from the literature is scarce. Only for S and assisted ventilation are similar values published (41.5 mmHg (S+M) and 42.7 mmHg (S), respectively [14]). A more differentiating equalization on this data is not possible because a minor pCO_2 could be explained either by M co-application [160] or by minor age [161,162].

Similar human data, as far as we know, do not exist for F in long-term sedation. Only experimental trials have shown that the pO_2 decreased significantly under F ($p<0.01$ and $p<0.001$, respectively) whereas the pCO_2 increased only on the level of $p<0.05$ [163,164]. Additionally, Dahan et al. demonstrated that the increase of pCO_2 is dependent from the dosage of F, but that such increase is clearly retrograde after a continuous infusion of 20 min and this even more in higher doses [165]. Although this is widely not understood until today, the results after 10 min [163], respectively the results after 20 min [166], cannot be transferred to a long-term sedation of ≥24 hrs. Declarations on the respiratory and metabolism state over more than 20 min are not admissible. Accordingly, in an animal experiment was found, for instance, that the glucose concentration was elevated after 1 hr and was decreased after 3 hrs [167].

This discrepancy could perhaps be resolved when we look to our correlation analysis. So the pCO_2 in F show not only a clear positive

coherency with the arterial pO_2 (r_S=0.615; p=0.033) but also a negative coherency with the serum glucose (r_S=-0.559; p=0.059). Because the p decreased to 0.009 (r_S=±0.713) when both parameters were combined one may the following assume: The pCO_2 is not only dependent on respiratory removal but also on O_2 delivery; impairment of the latter would decrease the pCO_2. If so otherwise the aerobic glucose metabolism is disturbed then also the production of CO_2 is diminished; simultaneously the glucose will not further decrease. Such effects should be overwhelming the restricted respiration removal when F is used.

Blood Pressure and Circulation

The pathophysiological alterations in sepsis and especially in septic shock are characterized by a reduction of myocardial pump output [62] as well as by diminution of macro- and microcirculation [168]. As such, the vessels on the one hand are maximal dilated, on the other hand, a demand adequate regulation is no more secured. Hereby the levels of catecholamines are elevated in the early phase of sepsis [169], but otherwise, the response to endogenous and exogenous vasopressors is not adequate.

Furthermore, an absolute and a relative volume deficiency usually occur in the frame of sepsis. Responsible for is an altered distribution caused by a venuous pooling and/or is an intravasal liquid loss by increased capillary permeability. Such baseline conditions were comparable in both uses, and the deficits were compensated by external fluids in the same extent (mainly cristalloids). In this concern was shown that aggressive fluid resuscitation during the first 48 hours of sepsis improved not only heart rate variability; moreover, this improvement correlated with survival [106]. Likewise, the application of catecholamines was similar in both groups (mainly norepinephrine). A higher dosed administration was not indicated because the already achieved effect could not be further enhanced; and enforcing a hyperdynamic circulation makes not really sense [168,170,171].

A so reduced cardiovascular function as is demonstrated in the F use is much often referred to a depression of centrally mediated sympathetic activity [172]. Accordingly, several investigations have shown that hemodynamic instabilities like bradyarrhythmias and blood pressure decrease can be connected with an application of opioids [28]. Such side effects are either mediated by a sympathetic inhibition and/or by a vagal stimulation [173,174]. However, concentrations of norepinephrine do not adequately represent

sympathetic activity in sepsis [175]. In this concern LF/HF ratio or LFnu in spectral analysis of HRV should be more suitable for attaining useful information about sympathetic modulation [176] and outcome [49]. However, beyond such influences on central regulation, opioids exert also direct influences on the cardiovascular system. There are alterations on heart rate and blood pressure described that cannot be only due to central nervous effects [177]. As such, the ability of cardiomyocytes for contractation will be also directly reduced by an agonism at the κ- and δ-opioid receptor [178,179].

Despite the decrease in blood pressure and heart rate when opioids were given to rabbits in anaesthetic doses [180], we found a more reduced blood pressure under F than under S when patients were analgo-sedated upon the RSS of <4 in mean ($p=0.006$). In such concern also the cardiac output decreased under S only slightly, but significantly in the dog [181]. In other trials a negative inotropic effect was found in F [182], but not so in S [183]. Further a significant cardiodepression is described in humans after 200 µg F [184]. However, no direct comparison is possible because of methodical differences. Nevertheless, it can be supposed that the lower ascertained blood pressure is at least also due to hypoxemia [185].

Although the meaning of HRV in very low frequency power (VLF) is widely unsettled [186], nevertheless, there are hints that this frequency density is especially important for prognosis in patients with congestive heart failure [187] or COPD [154] as well as in sepsis [99,188]. As such, in several investigations even the VLF power after ln-transformation was the the strongest predictor of outcome [99,189], and a coherence of oxygen supply/delivery and VLF fluctuations can by thoroughly assumed [190]. However, whether a residual peripheral vasoconstriction in sepsis should be considered by a different response of angiotensin under hypoxemia [151], this would be plausible in the sense of a centralization, but until now it is only speculative. Therefore, with regard to our results we would point to the stronger depression of VLF power under F ($p=0.006$) as well as to the only correlation of SO_2 and systolic blood pressure under S ($r_P=0.626$, $p=0.03$). Simultaneously, also the VLF (ln) correlated with the systolic blood pressure in supposal of a perhaps residually evident renin-angiotensin-aldosteron modulation [98,191,192] ($r_P=0.736$; $p=0.006$), but not when F was used (n.s.). However, a similar connexion of blood pressure and LF/HF ratio, as was reported in the onset of sepsis [193], we did not find in none of both therapy courses.

Heart Rate and Heart Rate Variability (HRV)

An impending cardiac failure often is concealed by an apparently normal cardiac output in sepsis [194]. Simultaneously, a broad autonomic dysfunction as could be shown in reduced HRV is endangering the patient [168]; hereby reduction correlates with severity of multiple organ dysfunction syndrome (MODS) as well as with prognosis [99,194]. Therefore, analysis of HRV as a non-invasive surrogate parameter is getting to more interest in intensive care medicine [57,99,188,195]. Coming from sepsis not only the size of HRV diminunition should be of only relevance, moreover, especially two parameters can be recommended in sepsis by respective results when severity of impairment and extent of risks is to examine. There is at first the LF/HF ratio <1 [48,49] and secondly the ln-transformed VLF component ≤3.9 [99,188].

As is well known, notably the autonomic functions are already reduced on the ground of sepsis and then especially such that are associated with sympathetic activity and are favoring the occurrence of hypotension [176,196]. In this concern a burden by endotoxines had led to a reduction of beat-to-beat variability over the total spectrum of the HRV [197]. Otherwise the LF band was the best predictor for multiple organ failure [198] and the HF band was comparatively even higher when patients died later [199]. Furthermore, catecholamine levels were elevated at the beginning of sepsis and simultaneously the sympathetic cardiovascular modulation was low [193]; this can be interpreted as a negative feedback [170]. On such complex circumstances the HRV is potentially influenced by different drugs too [200,201]. As such, the analysis of HRV can give additional information on altered autonomic functions in analgesia and anaesthesia [202].

This is usually necessary because the reaction on opioids is individual and differs in patients in great extent [203,204]. However, several studies have shown uniformly that HRV will be reduced by F as well as by S. Hereby especially the sympathetic determined parameters are concerned; the vagal influenced ones are less changed. Subsequently, the LF/HF ratio or, respectively, the normalized parameters LFnu and HFnu are vagal accented [205-208]. So it can be considered that the effects on physiological markers are more due to sympatheticolysis than to vagal activation [173], and that heart rate on sinus node level in strong diminished sympathetic activity will be mainly modulated on lower figures by vagal activity; this is in consense with results after bilateral cervical vagotomy under F application [174]. As such,

the still preserved vagal parts in frequency and time domain (lnHF bzw. rMSSD) correlated with the net ascertained heart rate (F/S overall $p \leq 0.001$).

A more reduced sympathetic response, as was decribed for F, is not only expressed by a lower blood pressure (s. above) but also by a non-appearance of heart rate increase. Therefore, the lower LF/HF ratio under F was connected with a greater reduction of sinus node frequency in our investigation ($p=0.046$). However, a correlation between LF/HF ratio and blood pressure or between LF/HF and heart rate we did not found, neither in F nor in S use. By this can be concluded again that vagal parts of autonomic nervous system even in S are dominating the sympathetic parts. Residual sympathetic influences in both substances are of minor relevance. This is in contrast to spontaneously breathing volunteers [209]. Because the HRV under AS in any case will be reduced dependently from dosage [46,170,205-208], a sympathetic predominance (high LF/HF ratio) should be rather in accordance to insufficient doses and a vagal predominance (low LF/HF ratio) rather to overdoses.

Remarkably, under the condition of very similar depth of AS especially that both parameters were significantly different in F and S that in other studies were guiding in sepsis (LF/HF ratio and VLF component). As such, in HRV analysis a stronger vagal predominance was found in F ($p=0.014$). Concerning prognosis, several reports exist that a value <1 supports the diagnosis of sepsis [48] und then is associated with increased mortality [49]. Beyond of those data there are also some more pubished hints that a low HRV with a vagal accentuation should be a risk marker in intensive care patients in general [4751,210]. Accordingly, similar HRV figures were associated with increased intracranial pressure and decreased cerebral perfusion pressure during advanced brain death [211-215]. However, also in patients with severe heart failure the HRV in the LF band was no more ascertainable [216].

However, the vagal predominance (mean LF/HF=0.15 in F and 0.25 in S) in the investigated first 6-72 hrs must not deceive about the vagal activity that was absolutely very low in all cases (mean HF=6,8 $msec^2$ in F und 6,4 $msec^2$ in S in comparison to 975 $msec^2$ as a not-adjusted normal value [96]). As such, our results are not in contrast to the possibility on principle that an impairment of the cholinergic anti-inflammatory response [217,218] would have led to an exceeding immune reaction [168].

As is already mentioned above, the second relevant parameter in sepsis should be the VLF band in power density [99,188]. Thus, in patients with multiple organ dysfunction syndrome the $\ln VLF \leq 3.9$ was the best predictor of mortality [99]. Comparatively to our investigation, in that study always F

was used for analgesia and in 73% M for sedation, either alone or in co-medication with propofol; S was not used in any case. Accordingly to that data only on F, we found in our comparative study, that the lnVLF power was significantly higher in the S use (p=0.006). Furthermore, we found several parametric correlations between the VLF band and some other parameters (pO_2/FiO_2, SO_2, systolic RR; r_P=0.0626-0.736; p=0.006-0.03), but only in the S use. Otherwise, the reported cut of 3.9 was not reached in any case at the HRV minimum, even not under S. The highest value was 2.63 in one patient with S analgesia, whereas no direct comparison is possible, because, unfortunately, no F or M doses were reported in that publication. Similar held also true for glucose concentration and insulin support that both may have co-influenced the HRV [100,219-223].

Body Temperature

In order to escape from further cerebral impairment followed by hypoxemia or ischemia, the organism elicits a number of compensatory responses, (1) a progressive reduction in BT which is accompanied by a reduction in metabolic heat production, (2) a ventilatory stimulation, and (3) a hypoxic tachycardia in mild hypoxia, that converted to a bradycardia in extreme hypoxia [224]. As such, hypoxia-induced anapyrexia [224-226] may be beneficial owing to increasing the oxygen uptake and to decreasing the oxygen consumption as well; the importance of this response on survival was emphasized by several animal studies [227,228]. Moreover, Matsuoka et al. have shown that anemic hypoxia and hypoxic hypoxia evoke anapyrexia similarly; this suggests that a decrease either in arterial oxygen content or in arterial pO_2 should be capable for inducing anapyrexia [229].

Thus, temperature in restricted O_2 provision is downregulated [224-226] by avoiding or, at least, diminishing of energy delivering exoterm metabolisms [166,226]. In this, for instance, the aerobic glucose oxidation is involved. However, the provision of ATP by anaerobic glycolysis is unequally more ineffective and is also connected with worse outcome on the other side [230]. The energy yield then only amounts to 7% of the aerobic pathway [231]. As such, for reducing the energy demand in F not only a reduction of blood pressure and heart rate was found, but also a lower BT [232]; under continuous F infusion temperature decreases by 0.7°C within 20 min [233]. However, similar was ascertained in epidural application of S [234]. Hereby the thermoregulation, on principle, can be performed by a central hypothalamic

inhibition as well as by a peripheral vasodilatation [39]; but upon our data from correlation analysis temperature adaptation under S should be more centrally influenced.

Decrease of BT by an inadequate tissue oxygenation was also seen when F was used in abdominal aortic surgery [235]. Accordingly, BT in our study was in mean by 0.8 °C lower in the F group than in the S group ($p=0.015$). This corresponds to the reported decrease under continuous F infusion [233]. However, one must not overlook that the oxygen demand will be simultaneously reduced by diminishing the heart rate [224,236]. Furthermore, the O_2 consumption decreases by 10-13% in general, when the BT decreases by 1°C [237]. Both, indeed, would surely have had favorable influences on energy balance, but regarding to F it must be queried that such positive effects are equalizing the negative ones by hypoxemia.

Although the reasons for very slow HRV modulations are widely unknown [186], the ln-transformed VLF band, indeed, correlated in S with the systolic blood pressure modulation (s. above), but not, as should be rather expected, with the BT [97]. Instead of, we found an inverse connexion of BT with the lnLF power in frequency domain ($r_P=-0.649$, $p=0.022$) in S. This was only marginally expressed in F (n.s.). Overall, we have to point out that HRV in F was mainly positively associated with BT and in S was always negatively associated with BT. Such had become also evident in the global time domain parameter SDNN (F: $r_P=+0.545$ $p=0.067$; S: $r_P=–0.703$, $p=0.011$).

Energy Supply

During the hypermetabolic state in early hyperdynamic phase of sepsis the total body oxygen consumption is often increased [238]. Simultneously, energy generation increases to cope with greater metabolic demands that are needed to deal with the acute inflammatory insult [239]. However, when additional impairment of pulmonary function becomes present, no sufficient compensation of oxygenation and tissue perfusion usually will be reached, even if respiration is mechanically supported [62]. Accordingly to our data it can be assumed that the oxygen provision under F surely was not optimal. In such preconditions glucose should be more anaerobically metabolized so that more lactate should be formed [235,240]. Hereby, the lactate concentration should be gained to a maximum and afterwards lactate itself will be metabolized in substitute [241,242].

Delivery of lactate is also associated with higher mortality in sepsis [243]. Conversely, concentration will be diminished if lactate is used as alternative oxidative fuel for generating energy [244]. Hereby, the glucose defiency can be partially equalized. The question what metabolic pathway will be preferred is due to the prevailing substrate status (law of mass action), at which under aerobic situation glucose is mainly quoted for gaining energy. As such, in physiological condition the main part is fully metabolized aerobically to CO_2 and the anaerobic pathway to lactate is of more theoretical importance. However, this relation is shifted by hypoxemia as well as under anaerobic condition a greater portion of glucose is consumed (Pasteur effect).

Thus, the more the oxygen supply is reduced, for example by F, the more the anaerobic glycolysis is preferred. Simultaneously the glucose concentration is reduced in geater extent than under aerobic conditions. In consequence, the residual oxygen will be dependently from concentration gradient more and more used for getting energy aerobically from lactate. Because the provision of energy by anaerobic glycolysis is significantly less expressed than by complete oxidation in the citrate cycle and respiratory chain (47 kcal vs. 673 kcal) [98], and because the supplementary oxidative metabolism of lactate is only able to substitute the oxygen deficieny partially, we must suppose that under F less energy was provided than under S. In such conception the pCO_2 correlated with the pO_2 positively and with the glucose level negatively under F (combined: $r_S=\pm0.713$, $p=0.009$). With respect to such considerations not only the carbohydrates but much more the oxygen supply is the leading cause for the size of potential energy supply.

Another argument, that the organism is evading the increasingly reduced oxygen provision by an increasing use of anaerobic glucose degradation, i.e. that the energy supply is performed by certain rules [235], is the positive correlation of serum glucose and serum lactate in the use of F ($r_P=0.745$, $p=0.005$). In S no similar coherence was seen. Moreover, this would mean, that the influence by lactate producing microorganisms or by their endotoxin-induced lactate production [245], so far as is present, is overlayed in F by a metabolic lactate degradation.

This also surely means that lactate levels under S cannot be prognostically compared to that under F. On the ground of a more expressed anaerobic glycolysis a poorer outcome should be more expected by F [230] than it is notified by the lactate concentration alone. As such, in S we found, as is should be normal, a clear connexion between the lactate in serum and the respective hydrogen-ion concentration (negative $_{10}\log$ = pH; $r_P=-0.767$, $p=0.004$). In this concern should be marked on a recently conducted trial, that

a lactacidosis was more relevant for in-hospital mortality than a singular hyperlactemia [246].

Regarding to the agent-specific glucose metabolism in sepsis is evident from the literature that both glucose and glucoregulatory hormone levels should be elevated by S. This is accompanied by likewise elevated catecholamines [247]. By contrast, a F-dose dependent diminution of glucose concentration was not only found in children [248,249]. Also the glucoregulatory hormones as well as the catecholamines and their elimination products decreased [250]. In the conception of both a reduced O_2 supply/consumption and a reduced residual glucose level a likewise decreased pCO_2 can be thoroughly explained in F. Although this coherence cannot be proved in our investigation directly, the Spearman´s correlations of pCO_2 and pO_2 in F (r_S=0.615, p=0.033) and even more that of pCO_2 and pO_2/serum-glucose (r_S=0.713, p=0.009) underline this assumption (S: n.s.).

Nevertheless, also marked alterations in septic metabolism were found by S in an animal study [247]. As such, already an endotoxin-induced inflammation was associated with metabolic changes that are typically leading to an increase of glucose concentration. Additionally given opiods in high doses reduced this hormonal and metabolic response. As such, S induced an increase of insulin and catecholamines after endotoxin application. Simultaneously the concentration of glucose increased by 36%, whereas glucose increased by 95% when S was not given. Furthermore, the endotoxin induced elevation of BT was abolished and lactate increased.

With respect to potential HRV influences by different glucose metabolisms it must be considered that both elevated glucose levels and insulin application should be rather connected with a sympathetic predominance [100,219-223]. Because these respective parameters were higher examined in the S group, this can be also due to glucose or insulin; however, this was coupled with the use of F or S and therefore cannot be influenced separately. A correlation of serum glucose and LF/HF ratio we only found in S (r_P=0.758; p=0.004). Considering that this constellation is in contrast to that is problematic in sepsis (low LF/HF ratio), it cannot really surprise that a stress induced hyperglycemia was rather protective in septic shock [251]. However, similar associations we did not find according to VLF power density.

What must be Considered from the Correlation Analysis?

Basic data has proved that patient groups receiving either F or S were comparable. Also the aspired AS was similar both in the aim (RSS = 2-3) and in the result (RSS in mean 3.9 vs. 3.8). Although patients within groups surely are varying in several characteristics, nevertheless, it can be supposed that such differences are present in similar extent. But with little restrictions the patients can be estimated to be widely homogenous.

Therefore, from the correlation analysis can be basically concluded that central modulated regulations were more evident in patients receiving S than in that ones receiving F. This can be shown impressively by clear coherences of relevant physiological parameters with such HRV parameters that should be very important for outcome in sepsis (for example, pO_2 or systolic blood pressure as physiological parameters vs. LF/HF ratio or lnVLF as special HRV parameters). Such connexions are specifically distinct for S, (s. Table). By contrast, such differential figures characteristically for F were found in parameters that are reflecting the hypoxic situation overall (for emample, arterial pO_2 vs. pCO_2 and glucose vs. lactate in serum). Similar was absent in S.

Thus, overall we have to consider that figures on serum glucose and on pO_2 even after adjustment on ventilation frequency and FiO_2 were significantly higher in S than in F (p=0.005-0.023). Furthermore, we found several significant correlations of arterial pO_2 and serum glucose with the two most outcome relevant HRV parameters (LF/HF ratio and VLF component; p=0.004 – 0.04; s. Table). Although it cannot proved by the presented data, we must apprehend that the energy provision in F should be nearby the minimum. The clear positive correlations of serum glucose vs. lactate (p=0.005), of artrial pO_2 vs. pCO_2 (p=0.033), and of pCO_2 vs. pO_2/serum glucose (p=0.009), exclusively in F, are in accordance to this suppose.

Otherwise, it was already repeatedly supposed that especially the diminution of HRV should serve as a special sign for decoupling of complex physiological regulations [55-58]. Accordingly, a reduced HRV correlated significantly with scoring systems reflecting the severity of the multiple organ dysfunction syndrome [252]. Likewise, also measures of power spectra were inversely related to severity of illness and outcome in critically ill children. [195]. Therefore, it can be assumed that HRV analysis reveals additional information on vital risks and prognosis in real time [253]. This would mean that in the moment of maximal HRV depression the patient should be, perhaps acutely most, endangered [254]. For the therapeutic result it could be also

important, in what extent the autonomic functions, perhaps only temporary, are impaired [255]. Such ability of the involved end organ to respond appropriately to neural regulation is not only influenced by the illness itself, but also, for example, by anesthetics [256].

For an influence that cannot be ignored is prevailing that not only the LF/HF ratio is changed to pathologic figures [47-51], but also the activity in VLF fluctuations was both (1) more impaired under F than under S and (2) HRV correlated in this HRV component after ln-transformation with systolic blood pressure, arterial pO_2/FiO_2, and arterial SO_2 when S was used and not when F was used. In this concern it has been shown in other trials that even the fluctuations in the VLF band after ln-transformation had best prognostic relevance for survival in the first two months after incidence of sepsis [99,257]. However, in that investigation always F was used for analgesia and much often M for sedation. A correlation, by our data not surprisingly, was not mentioned; other opioids like S were not comparatively investigated.

Now the question arises whether even the very low frequent modulations should be prognostically relevant in greater extent. One may speculate that such activity in sum is perhaps representing the autonomic regulations that would react only slowly and not hectically on the occasionally changed demands. With respect to such potentially stabilizing effect, the VLF power was already related to temperture regulation, humoral and endocrine regulation, and regulation by the renin-angiotensin-aldosterone system [258]. Such interferences may be detectable in relative robust parameters; in multiple organ dysfunction syndrome or sepsis, respectively, such slow regulating effects could make prognostically good sense. Conversely, in orthostasis reaction more rapid adaptations are necessary.

Arrhythmie Inzidence and Outcome

On the one hand F has promoted some arrhythmias by a vagal overactivity [259,260]; on the other hand there exist several deseases in that even a sympathetic predominance is prognostically unfavorable [261,262]. Herein a parasympathetic effect may be advantageous [263-265]. In this concern no relevant differences between F and S were found in arrhythmogenesis. The incidence of supraventricular and ventricular ectopic beats was only slightly higher in F.

However, the question cannot be answered by the study, whether this incidence in both agents was really similar or whether the use of QTc

prolonging antibiotics/drugs has led to equalization in high level [115,116]. Nevertheless, it can be assumed that, certainly, the arrhythmic episodes excerted no important agent specific influences on outcome [168]. As such, the in-hospital mortality overall was not significantly different ($p=0.1$; SMR = 1.165 in S and 0.648 in F, respectively).

By contrast, this was not so in non-survival under continuous infusion of AS or in the overhang, i.e. until 2 days after end of F or S infusion ($p=0.025$). Thus, four patients under F died because of bradycardic circulatory failure (2x), because of arrhythmogenic cardiovascular failure or because of asystole (complete AV block). The other three ones (2 F, 1 S) died by respiratory failure. At that time, for instance, the oxygenation was significantly lower performed under F than under S ($p<0.025$). Already this more anaerobic metabolic state as well as the lower mean blood pressure in F ($p=0.006$) can thoroughly explain the higher ascertained mortality [83,84] despite the fact that patient size (2x12) is only low. Accordingly, hemodynamic effects by S in patients with ischemic heart disease were described only in minor extent; the left-ventricular function was not worsened [183].

Limitations

As is also demonstrated in the Table, there are especially three parameters that are different between F and S: M application/kg ($p=0.008$), glucose concentration in serum ($p=0.01$) and Insulin application ($p=0.001$). Those characteristics may have had an additional and releveant influence. However, because those differently ascertained parameters are coupled to F or S therapy, the question is only arising theoretically, how far the results are really due to that special parameters. Nevertheless, such potential influences are discussed as follows.

A worth mentioning muscle rigidity was not examined by GABA agonists even in high dosage [39]. Furthermore, in another investigation the F induced thorax rigidity was reduced by M [160]. Conversely, arterial blood pressure, cardiac output, stroke volume, and systemic resistance were reduced by M in another study [84]. Indeed, those alterations should be low estimated in the healthy surely, but in combination with opioids such can become relevant because of CYP3A4 interaction [266-268]. Unfortunately, on this item no information is possible because no concentration measurement was conducted. In HRV analysis a reducing effect by M over the whole spectrum of frequencies is published repeatedly [134,138,144,269]. Simultaneously,

changes in sympathetic-vagal balance were not always the same. Prevailing is a rather vagolytic influence; but sometimes the LF/HF ratio remained also unchanged [270].

Otherwise, also glucose and insulin exert influences on HRV and blood pressure. Higher glucose and insulin concentrations may elevate the LF/HF ratio [220] as well as the blood pressure [221]. Accordingly, vagal activity in patients with pre-diabetes [100] and even more in diabetic patients [219] or by glucose concentrations of 10-18 mmol/l is decreased [223]. Therefore, in relatively low hyperglycemia and adequate insulin application rather a sympathetic predominance with blood pressure increase is to expect [222]. Such effect can be accompanied in S analgesia [247].

Furthermore, patients could not be exposured for examination the increase of intracranial pressure [271,272] as well as the decrease of cerebral perfusion pressure [273] that both may have been differently influenced by F and S. Also the question is open, how the catecholamine administration must be estimated. As such, in a recently published study with healthy volunteers receiving endotoxin and partly epinephrine for 9 hrs was shown that the HRV parameters were further reduced by epinephrine; however, with respect to LF/HF ratio no uniform figures were detected [274]. Moreover, conclusions on critically ill patients on later priods by a simultaneously performed therapy are not permissible on that ground.

Now a look to cumulative aspects. In titration on a clinical aiming point the different cumulative effects of F and S are at first without relevance. However, regarding to specific contextsensitive half live periods [12] the results of our study cannot be simply referred to later phases of dose reduction. Further, it could not be the primary aim on already clinical aspects to awaken the patient in the first phase of sepsis. This is in accordance to other reports [33]. And phases of cinical recovery and weaning were not the topics of the investigation; such also could not be, because 50% of the F patients had already died under AS or shortly afterwards. Further is well known that weaning and recovery are more retarded under F than under S [15,16].

The results of septic patients, of course, cannot be simply translated to other collectives. Less severe ill patients and diseases that are associated with a more sympathetic prevalence must be valued separately. Also because sepsis must be considered as a 2-phased process [169], our results from the initial hyperinflammatory phase cannot be transferred to the later phase of immunoparalysis. Nevertheless, an additional loss of control mechanisms that are apparently more expressed by F than by S, may accompany to further, at least functional, impairment of organism.

Conclusion and Outlook

Basically to centrally induced muscle rigidity, it must be considered that a diminished provision of oxygen may contribute to worse outcome. As such, our data show that respiratory depression was more expressed by F than by S, even when patients received ventilatory support. That this is really relevant is demonstrated by clear coherences of aterial oxygen, CO_2 origin, serum lactate and serum glucose when F was used. In S such associations were not found.

Instead of, even the two parameters that were most relevant for outcome (LF/HF ratio [48,49] and VLF component of Power [99]) were (1) significantly higher in the S group and (2) correlated significantly with several critical parameters in the S group that were (3) also significantly higher found in the S group (pO_2, SO_2, blood pressure). (4) In the F group no such clear coherences were found. This can be mainly explained by greater sympatheticolysis on the ground of relatively more preserved vagal effects.

As such, the mainly sympathetically caused influences on heart rate and blood vessels should be more reduced by F than by S. This then would also mean that general conclusions from F to other opioids such as S are less serviceable. As such, the conducted analysis of correlations prevailed arguments that autonomic dynamics are more preserved in S. In F more static and stiff coherences between physiological markers were found. By contrast, no central regulatory mechanisms like in S became evident. This argues for a widely abrogated reflex response in F. This expression should be so strong that antagonisations by naloxone revealed no effects anymore [268,275].

Although mortality under AS was also consistently lower in the S use, we must consider that the patient size (2x12 patients) is low. However, the multiple interactions/non-interactions of autonomic nervous system parameters with outcome relevant parameters may underline the outcome result. In the conception that cardiac functions under F would be performed widely uncoupled, such constellations were suggested to be responsible for occurrence of septic shock [57] as well as for poor outcome [274].

Likewise, the data show, that the analgesically equivalent doses were higher in the S use, although it cannot be really assumed that the patients would have endured a greater dose of F. Therefore, it can be well concluded that an AS with S is surely not inferior to an AS with F; however, a greater analgesia is possible with S.

Beyond the results in the close concern, the investigated interferences show that a series of endangering factors is gathering in sepsis or in respective therapy. First, there is the septic process itself [109,276] further leading to

multiple organ failure [99]. Additionally, specific influences caused by antimicrobial drugs must be supposed [107], likewise by analgesics and sedatives [203,205-207]. Not to neglect that one should also reflect on catecholamines in dependence from infusion duration [274], and to euvolemic replacement [106] and to interactions with CRP as well [105].

Already this enumeration illustrates that the circumstances in sepsis are very complicated. If we want some more knowledge in this problematic field we must look for singular effects first in healthy subjects [208]. Only if sufficient information is available to all that points, an individually adequate therapy can be choosen. So far one must rely on experiences of the practice, well knowing, that such more weak decisions are not always optimal. In any case further additional comparative studies on AS are needed [277].

Likewise there are several reports that a hyperglycemia should be a special risk factor in general [101,278,279]. By contrast recently was stated that a stress induced hyperglycemia acted rather protective in sepsic shock [251]. This and our results should give reason for requestioning also the importance of especially higher glucose levels in the sepsis.

Conflicts of Interest

None declared.

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