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Reduction of the bacterial load by the silver-coated endotracheal tube (SCET), a laboratory investigation *

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Abstract. Microaspiration enabled by high-volume-low-pressure cuffed endotracheal tubes is the most likely explanation for ventilator-associated pneumonia. To decontaminate the secretion at the proximal end of the cuff we developed a silver-coated endotracheal tube (SCET). In an *in vitro* model we investigated the efficacy of SCET to lower the bacterial load of secretion and aspirate. We developed a continuously contaminated and mechanically ventilated oropharynx–larynx–lung model to investigate the reduction of the bacterial count by SCET compared to controls. The model was continuously contaminated via the oropharynx–larynx with *Pseudomonas aeruginosa* ATCC 27853. During the investigation period of 50 hours the bacterial count of oropharynx–larynx and lung was measured as colony-forming-units/ml. In addition, the characteristic curve of silver ion release of SCET was determined. SCET significantly reduced the bacterial count in oropharynx–larynx at all timepoints ($p < 0.05$). In lung the bacterial count was significantly lower beginning with the 36th hour of recording ($p < 0.05$). A reduction of greater than 2 log was found from 28 hours on in oropharynx–larynx and from 50 hours on in lung. The release of silver ions was very rapid and was described by a mono-exponential function with a time-constant τ of about 60 minutes and a saturation concentration of $200 \pm 80\ \mu$g/l. SCET showed a significant inhibition of growth of *P. aeruginosa* in the continuously contaminated and mechanically ventilated oropharynx–larynx–lung model. SCET by thus might be helpful in reducing ventilator-associated pneumonia.

Keywords: Ventilator-associated pneumonia, decontamination, aspiration, microaspiration, antimicrobial activity, silver, silver-coating, endotracheal tube, silver-coated endotracheal tube, SCET, characteristic curve

1. Introduction

Ventilator-associated pneumonia is one of the main reasons for the high morbidity and mortality in ICU patients [1]. Its incidence ranges between 9 and 70% [1–3]. Besides the physiological and immunological status of the patient three main sources of lung infection are discussed, (1) septic foci, (2) translocation of bacteria through the intestinal wall, and (3) aspiration of contaminated oropharyngeal and gastrointestinal contents in the presence of a cuffed endotracheal tube [4–11]. Endotracheal tubes are nowadays equipped with a high-volume-low-pressure cuff, known to be associated with leakage along folds created by the inflated cuff [12,13]. Even cuff pressures of 60 cmH_2O do not prevent this leakage as shown in an *in vitro* model [14]. Attempts have been made to lower the risk of microaspiration by reducing

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the bacterial load of the oropharynx. Both continuous subglottic suction [15,16] and local administration of antibiotics [17] were shown to lower the incidence of ventilator-associated pneumonia. For the same purpose many centres routinely perform lavage of the oropharynx with chlorohexidine or betadine. This, however, basically requires significant manpower as well as sedation and relaxation during weaning. To reduce the amount of oropharyngeal–laryngeal microorganisms without the requirements of additional interventions we designed a silver-coated endotracheal tube (SCET) (United States Patent 5,725,510, European Patent 0699081, Hartmann et al.) to continuously decontaminate the oropharynx. Silver has long been known to act as a disinfectant with low toxicity to human tissue [18]. Other authors demonstrated its antibacterial [19–24], antiviral [25,26] and fungicidal [27] properties. Depending on its concentration, silver was shown to be bacteristatic or bactericidal [22]. It was investigated as a solution [19], complexbound in soluble molecules [28], layered on medical devices [29–31] or fabrics [32] or electrically activated [22,31,33]. Most recently, the antimicrobial efficacy of silver-containing intravascular catheters has been demonstrated [30,31]. Since the bacterial load of the oropharynx is high, a high concentration of silver ions for its decontamination is required. Estimations of the concentration of silver ions needed to achieve an antimicrobial effect in the oropharynx [34] as well as own preliminary studies on the release of ions of the spattered silver coating have suggested that the concentration of silver ions provided will be adequate as well as non toxic to human tissue when a silver-coated endotracheal tube is used.

The purpose of this study was to investigate the antimicrobial effect of SCET in an *in vitro* model. We developed an oropharynx–larynx–lung model which was continuously contaminated with *P. aeruginosa* and which for the purpose of clinical simulation was mechanically ventilated.

2. Methods and materials

2.1. The model

Figure 1 shows the design of the continuously contaminated and mechanically ventilated oropharynx–larynx-lung model. The model was designed, (1) to simulate anatomical structures which take part in the act of microaspiration and, (2) to simulate the dynamic forces on the cuff of the endotracheal tube during mechanical ventilation. It was made of polymethylmethacrylate (plexiglas). The model consisted of, (1) a chamber representing the oropharynx and larynx (ORO), followed by (2) a tube with a diameter of 17 mm representing the trachea [35], and (3) a second chamber representing the lung (LUNG).

ORO was filled with 200 ml of bacteria-containing medium. Additional bacteria-containing medium was continuously pumped into ORO by a peristaltic pump (INFUSOMAT II, Braun, Melsungen, Germany) through an inlet in a lid covering ORO for protection against contamination by room air. The added liquid to ORO either passed along side the inflated cuff of the endotracheal tube into the LUNG liquid or it was drained via an overflow outlet. Prior to sampling of ORO liquid a peristaltic pump acting as an agitator pumped liquid from an outlet located at the bottom of ORO to a second inlet located in the cover. Though magnetic stirring was technically impossible due to the geometric dimension of the model own preliminary investigations had shown that homogenization by such an agitator prevented sedimentation of viable or inhibited bacteria. A 6.0 mm ID endotracheal tube (SILKOMED® Silkowave 100, RÜSCH, Kernen, Germany) was introduced into the tube connecting ORO and LUNG. The cuff was inflated to a constant pressure between 36 and 42 mmHg by means of an external reservoir of pressurized air. The cuff pressure was monitored on-line (EAGLE 4000, Marquette Electronics, Paris, France).

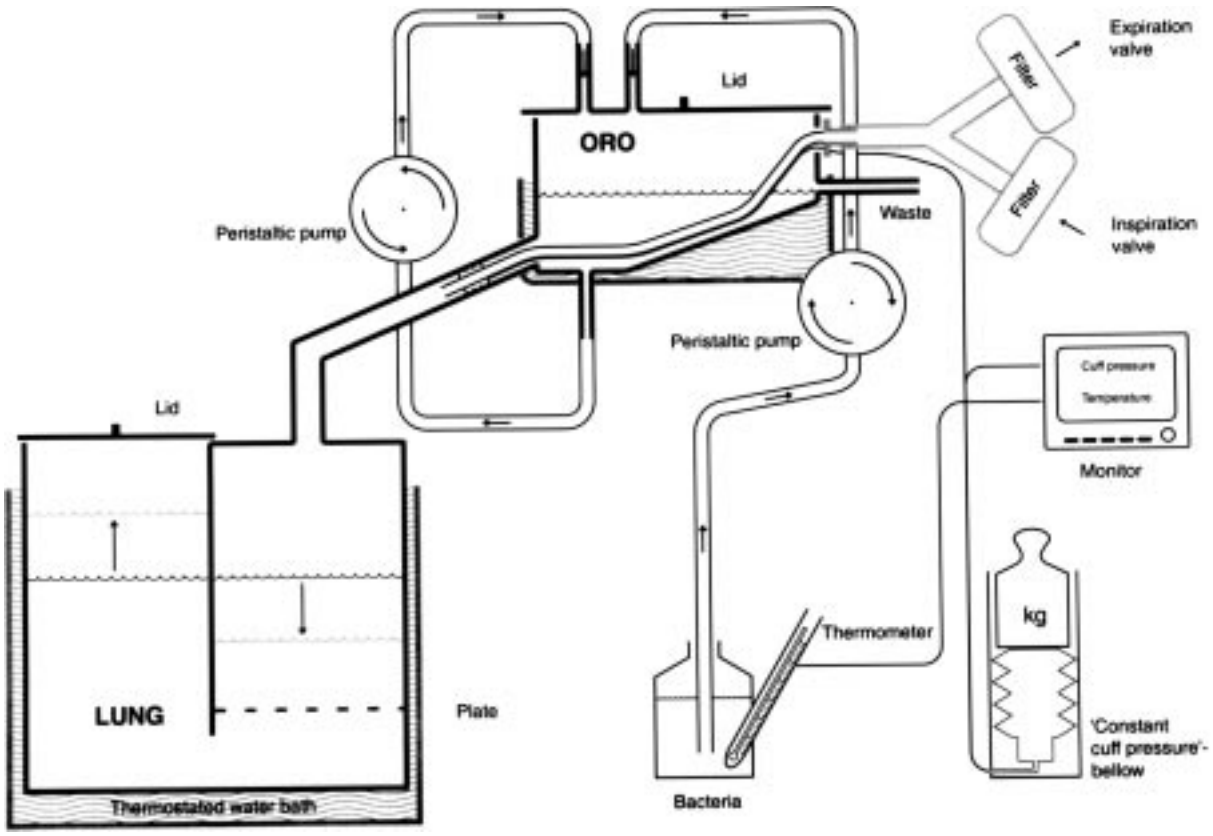

Fig. 1. The continuously contaminated and mechanically ventilated oropharynx–larynx–lung model. ORO = oropharynx–larynx; LUNG = lung. For further details see text.

LUNG was ventilated in the volume-controlled mode via the endotracheal tube with a ventilator (ERS 300, Engström, Stockholm, Sweden). Bacterial filters were inserted into the inspiratory and expiratory limb of the respiratory tubing system. The ventilator produced a tidal volume of 300 ml, and a PEEP of 1 cmH_2O. In reference to Guttmann et al. [36] LUNG consisted of a two-chamber tank of a total volume of 3500 ml filled with 2000 ml of medium. If the ventilator delivers a gas volume via the endotracheal tube into the model, the corresponding liquid volume is displaced into the chamber which is open to atmosphere. The resulting change in pressure equals the hydrostatic pressure exerted by the displaced water column. The difference in height of the water surfaces in the two adjacent chambers gives the change in pressure in cmH_2O. The geometric dimensions of the model were chosen to achieve a constant compliance of 50 ml/cmH_2O. A plate containing 64 boreholes with a diameter of 1 cm each prevented the water column from large oscillations and simulated a flow resistance of 2 cmH_2O/l/s. To protect the medium against contamination by room air LUNG was covered by a lid.

A constant temperature of 37°C was provided by a thermostated water bath (C6 CS, Lauda, Lauda-Koenigshofen, Germany). Inlet and outlet of the thermostated water bath were connected to the ORO level while an overflow-outlet was connected to the LUNG level (not drawn in Fig. 1). Between the two levels the water was circulated by two centrifugal pumps (KRP 800, Heidorf, Kehlheim, Germany) connected to work in an opposite way.

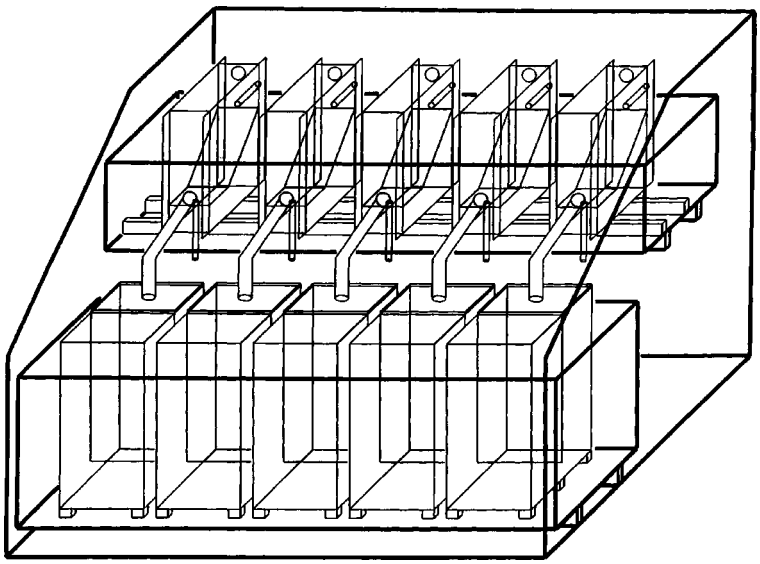

Fig. 2. The continuously contaminated and mechanically ventilated oropharynx–larynx–lung model. Five identical units are connected in parallel. Top chambers = oropharynx–larynx. Bottom chambers = lung.

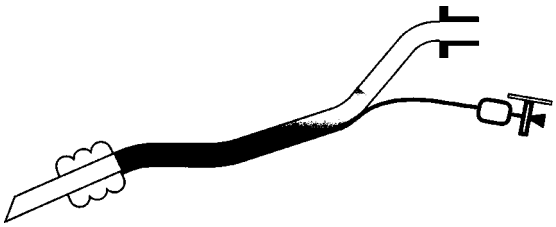

Fig. 3. The ID 6.0 silver-coated endotracheal tube (SCET). The coating is spread over a length of 17 cm.

There were five identical units, each consisting of the oropharynx–larynx chamber, the trachea, and the lung chamber. They were labeled "I" to "V" and connected in parallel. This set-up enabled simultaneous evaluation of five endotracheal tubes (Fig. 2).

2.2. The silver-coated endotracheal tube (SCET)

To obtain SCET an endotracheal tube of 6.0 mm ID (SILKOMED® Silkowave 100, RÜSCH AG, Kernen, Germany) was covered under vacuum with 0.15–0.25 μm thick silver films after pre-coating with different precious metals. Own preliminary studies using repeated dynamic forces on such a coating exclusively led to fissures without any peeling off. This coating is used by the same manufacturer for commercially available urinary tract catheters. On SCET it starts proximately to the cuff and extends for a length of 17 cm (Fig. 3). For each investigation 3 SCETs and 2 control tubes were placed in either of the five units in random order.

2.3. Bacteria and medium

P. aeruginosa ATCC 27853 was used. Preliminary studies had shown that PBS is the optimal medium for providing constant concentrations during the 50 hours test period. PBS consists of 0.1 g/l $CaCl_2$,

0.2 g/l KCl, 0.2 g/l KH_2PO_4, 0.1 g/l $MgCl_2 \times 6\ H_2O$, 8.0 g/l NaCl and 2.16 g/l $Na_2HPO_4 \times 7\ H_2O$. With a photometer the inocula were adjusted between 1.0×10^3 and 1.0×10^4 cfu/ml (colony forming units/ml PBS) and checked by agarplates (DST Agar, Oxoid/Unipath, Basingstoke, Great Britain). The additional bacteria-contaminated PBS was stored at $+4$ to $+12^\circ$C under on-line temperature control using a monitor (EAGLE 4000, Marquette Electronics, Paris, France), and continuously stirred. Own preliminary investigations revealed that the bacterial count shows stable concentrations under the beforementioned conditions. A peristaltic pump delivered 100 ml/h of bacteria-contaminated medium to the entire five-unit model. By means of five 3-way stopcocks the infusate was directed to each ORO at a rate of 20 ml/h. This inflow volume either substituted for the leakage along side the cuff or was drained.

2.4. Sampling procedures

Prior to sampling the liquid contained in ORO was "stirred" for two minutes by the agitator. Samples of ORO and LUNG were gained with a pipette after lifting the lids. Two-ml samples of liquid were taken at 2, 4, 6, 12, 20, 28, 36, 44 and 50 hours, after the start of the experiment. Samples were stored at 4°C and processed within 12 hours using a semiautomated method (C 40 Plater, Meintrupp Labortechnik, Lehden, Germany). The diluted sample was aspirated by the apparatus and subsequently spread spiral-shaped on agar-plates. After 48 hours of incubation the colony forming units per ml sample liquid (cfu/ml) were determined by personnel. The limit of detection was less than 27 cfu/ml. Subsequently the logarithm ($\log_{10}$) was calculated. Every sample was investigated for contaminating environmental bacteria. Contaminated samples were excluded.

2.5. Determination of the silver ion concentration

The concentration of silver ions was determined by graphite furnace atomic absorption spectroscopy. All measurements were performed in triplicate. In a model using a glass cylinder filled with sterile normal saline we determined the 24-hours elution of silver ions of SCET and the characteristic curve of silver ion release by SCET. All samples were initially filtered by a 0.2 μm membrane.

2.6. Sterilization

Prior to each investigation the model was rinsed with tap water and subsequently sterilized by gamma irradiation using 16.20 kGy. Though the dose was reduced due to the expected damage of plexiglas by repeated gamma irradiation we could proof sterile conditions. The lids and connectors were plasma sterilized according to recommendations of the Institute of Environmental Medicine, Freiburg University Hospital. All SCETs and controls were sterilized by gamma irradiation. The ventilatory equipment was autoclaved at 120°C.

3. Statistic section

Due to the unavoidable formation of clusters caused by the fact that in each experiment five tubes were contaminated by one particular inoculum a non-parametric test was applied. The difference in bacterial count between SCET and controls was tested using the Kruskal–Wallis test in the modification of Haux, Schumacher and Weckesser [37]; $p < 0.05$ was considered statistically significant. The Holm correction for repeated measurements was applied.

To evaluate clinically significant reduction of the bacterial load, absolute numbers were used. To take into consideration the exponential bacterial growth $\log_{10}$ was calculated for all data. Results below the limit of detection (less than 27 cfu/ml) were assumed to be 10^1.

The concentrations of silver ions are presented as mean values.

4. Results

4.1. Bacterial count

14 SCETs and 9 conventional endotracheal tubes were investigated. 181 observations could be analysed. None of the samples had to be excluded due to contamination.

In general, the bacterial count (cfu/ml) in ORO was significantly lower when a SCET was used. Since nearly all bacterial counts in ORO were lower, significance was shown ($p < 0.0005$ at 2, 4, 6, 12 and 20 hours; $p < 0.005$ at 36, 44 and 50 hours; $p < 0.05$ at 28 hours). In LUNG the bacterial count was significantly lower beginning with the 36th hour of recording ($p < 0.05$).

Table 1 lists the results of representative experiment.

In ORO a reduction of the bacterial count of greater than 2 log was achieved from 28 hours on (Fig. 4, left). In LUNG a reduction of greater than 2 log was achieved from 50 hours on (Fig. 4, right).

4.2. Silver

The elution tests showed reproducible concentrations for every 24 hour period during 4 days. The average daily eluate in 100 ml of normal saline for the 3 SCETs (A, B, C) contained 202±3.2, 159±45.3, and 176 ± 28.7 μg/l, respectively (Table 2).

Analysis of 6 SCETs revealed a rapid release of silver ions, which is mathematically described by

$$[\mathrm{Ag}^+](t) = [\mathrm{Ag}^+]_\infty(1 - \exp\{-t/\tau\})$$

Table 1
Original chart of one experiment (no. 2 out of 5 experiments)

	ORO[1]					LUNG[2]				
	I[3]	II	III	IV	V	I	II	III	IV	V
	Control[4]	Control	SCET[5]	SCET	SCET	Control	Control	SCET[5]	SCET	SCET
2 h[6]	2.4×10^3 [7]	2.3×10^3	432	1.1×10^3	1.6×10^3	<27	27	27	405	270
4 h	1.0×10^3	1.0×10^3	<27	<27	27	54	81	<27	<27	27
6 h	1.8×10^3	1.2×10^3	<27	81	1.1×10^3	<27	27	27	<27	<27
12 h	1.2×10^3	2.0×10^3	108	27	486	27	<27	27	<27	<27
20 h	6.6×10^3	1.2×10^3	27	54	27	<27	27	<27	54	<27
28 h	1.4×10^3	871	27	3.2×10^3	<27	<27	<27	81	27	<27
36 h	8.8×10^4	5.5×10^3	54	378	<27	<27	270	<27	27	<27
44 h	1.7×10^5	4.6×10^5	297	1.5×10^3	135	<27	324	27	162	<27
50 h	1.4×10^5	1.2×10^5	729	1.9×10^3	243	162	2.0×10^3	<27	1.4×10^4	<27

[1] Oropharynx–larynx chamber; [2] lung chamber; [3] unit number 1 out of 5 units; [4] non coated endotracheal tube; [5] silver-coated endotracheal tube; [6] sampling time points; [7] cfu/ml phosphate buffered saline.

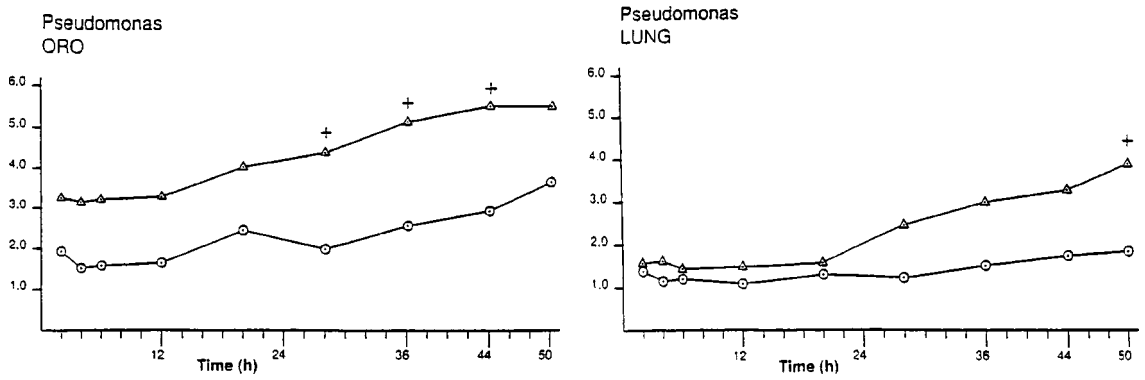

Fig. 4. The reduction of the bacterial load by SCET. Expressed as mean logarithms of colony forming units/ml. ∘ = SCET; Δ = control. A difference greater 2 log is indicated by +. Left = Oropharynx–larynx. Right = Lung.

Table 2
24-hours elution of silver ions of three SCETs in 100 ml normal saline in the bench top model

	SCET A	SCET B	SCET C
1st 24-hours elution [Ag^+][a]	198	171	172
2nd 24-hours elution [Ag^+]	205	210	196
3rd 24-hours elution [Ag^+]	204	101	137
4th 24-hours elution [Ag^+]	201	153	199
	202 ± 3.2[b]	159 ± 45.3	176 ± 28.7

[a] Concentration of silver ions in μg/l. [b] Mean $\pm$ SD.

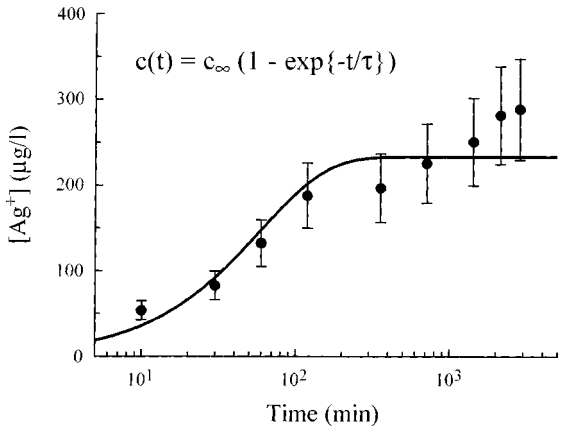

Fig. 5. The characteristic curve of the silver ions release of SCET. Measured data were mathematically approximated to the equation depicted in the diagram. Concentration of silver ions in μg/l normal saline. [Ag^+] = concentration of silver ions; τ = time constant.

(Fig. 5). Already by 10 minutes, concentrations of more than 50 μg/l were determined at the first use of SCET. The time constant τ is about one hour and the saturation concentration $[Ag^+]_\infty$ is $200 \pm 80\,\mu$g/l. Both coefficients did not change with repeated use of SCET (data not shown here).

5. Discussion

The silver-coated endotracheal tube (SCET) significantly reduced the growth of *P. aeruginosa* in the continuously contaminated and mechanically ventilated oropharynx–larynx–lung model. The bacterial count in the oropharynx–larynx chamber (ORO) was lower throughout the whole investigation period of 50 hours.

In the lung chamber (LUNG) the bacterial count which represents microaspiration became significantly lower after 36 hours for the remainder of the experiment when SCET was used. Since the aspirate was diluted, the amounts of bacteria were close to the detection limit during the beginning of the experiment.

To evaluate the microbiologic implications of our results a reduction in bacterial count of 2 log was considered clinically significant. Such a reduction of 99% or even more was found in the continuously contaminated oropharynx at 28, 36 and 44 hours, respectively, and in the lung at 50 hours.

This efficacy has to be viewed in respect to the required fixing of the results below the limit of detection. In fixing these results by 10 cfu/ml instead of 1 cfu/ml we chose the disadvantageous case.

As we knew from preceding investigations it is difficult to find a medium that avoids growth of *P. aeruginosa*. PBS appeared to be suited best. Nevertheless, growth tends to increase dramatically after 24 hours independent of the surrounding temperature. The original recording illustrates the increase of bacterial counts in ORO and LUNG during constant contamination, however, at any rate it shows the efficacy of SCET (Table 1).

Our model enables (1) simulation of the microbiological environment in both the upper airways and the lung, and (2) simulation of mechanical ventilation with realistic dynamic forces acting at the cuff wall and by thus (3) simulation of microaspiration. The proximal part of the endotracheal tube was submerged in contaminated liquid. This liquid reservoir had a constant bacterial inflow, and an overflow opening thus simulating continuous contamination. The model lung was mechanically ventilated in the volume-controlled mode via the endotracheal tube. Pulmonary mechanics, i.e., respiratory system compliance and resistance, were simulated by means of a two-chamber liquid-filled tank with a constant compliance of 50 ml/cmH_2O and a constant resistance of 2 cmH_2O/l/s. During mechanical ventilation the cuff wall of the endotracheal tube was dynamically stressed by forces changing with respiratory rate. All liquid reservoirs within the model were thermostatically-controlled saline solutions that are well suited for bacteriological investigations. The model showed no contamination by foreign bacteria though LUNG was partially open to atmosphere.

All tested endotracheal tubes, SCET or control, always showed a leakage along the side of the continuously pressure-controlled inflated cuff. This has recently been shown to occur in rigid tracheas *in vitro* [14]. To prevent large volumes of aspirates from leaking alongside the cuff, we selected an unphysiologic high cuff-pressure between 36 and 42 mmHg. Even such high cuff-pressures did not prevent leakages at a peak airway-pressure of 15 cmH_2O and a PEEP of 1 cmH_2O. Although ventilator settings remained unchanged, the rate of leakage across a particular tube varied during the investigation. Most probably this was due to changes of the folds and consecutive changes of hydrostatic pressure above the cuff.

Since ventilator-associated pneumonia is a well known problem in ICU patients several attempts have been made to lower the bacterial load of the pharyngeal and subglottic secretions. Mere suction of subglottic secretion and the oral application of antibiotics have been shown to be effective in decreasing the incidence of ventilator-associated pneumonia [15–17]. Rinsing of the oropharynx with disinfectants is a wide spread routine. However, these maneuvers require additional personnel and interfere with the

patients' weaning. To circumvent all of the forementioned problems, SCET was developed. We hypothesized that a continuous emission of silver ions could reduce the bacterial load of the oropharynx including the assumed gastro-intestinal reflux. Furthermore, due to aspiration and microaspiration, we expected the contamination of the lung compartment to be lower. In our *in vitro* model investigating *P. aeruginosa* this hypothesis could be confirmed.

In the human oropharynx there are 10^8 to 10^9 bacteria/ml [38]. To reach a bactericidal effect, in one single *E. coli* bacterium 6×10^5 and in a single coccus 10^7 silver ions, respectively are needed [34]. Based on theoretical estimations we assumed that silver ions in a concentrations between 20 and 200 μg/l (which equals ppb) have to be provided. This is consistent with the reported efficacy of silver in a concentration range of 50–500 μg/l [39].

A commercially available endotracheal tube was coated with a 0.15–0.25 μm silver film proximal to the cuff (Fig. 3). Elution tests showed reproducible concentrations for every 24 hours period within 4 days. Previous experiments with time steps of 6 hours showed the saturation concentration already being reached after a few hours.

The effectivness of silver in reducing bacteria is dependent on the concentration of silver ions $[Ag^+](t)$, which in turn depends on application time. In the beginning $[Ag^+]$ is zero and after an infinite time it reaches the saturation concentration $[Ag^+]_\infty$, since the silver reservoir is infinite with respect to the silver amount in the solution. In our investigation the starting level was always below 0.1 μg/l, a value determined by the accuracy of this method. The characteristic curve revealed (1) a saturation concentration which is in good accordance to the previously mentioned antimicrobial activity and, (2) a time constant which indicates that 60% of the saturation is achieved within one hour (Fig. 5). The saturation concentration is comparable with the solubility of silverchloride in water [18] but is higher than expected in respect to maximum solubility of silver ions in normal saline (see below). In relation to the delivered silver ions the amount of silver provided by SCET is infinite. Both saturation concentration and time constant remain almost unaffected by multiple use. Hence, the generation of silver ions is high enough and fast enough to be effective in reducing the bacterial load.

We believe that the saturation concentration crucially depends on the quality of film preparation, experimental setup and temperature. It should be kept in mind that these measurements were performed at room temperature ($20 \pm 2^\circ$C). Thus, under physiologic temperatures these values can be expected to be higher.

We assume that even the high bacterial load in the oropharynx can be treated by the provided silver. A successful inhibition of 10^7 cells *P. aeruginosa*/ml by silver ions was shown previously using silver ion concentrations similar to the one provided by SCET [40]. However, it was stated that with higher bacterial concentrations it takes a longer time to reduce the bacterial count while initially low cell concentrations hasten the silver ions effect.

The question arises if one has to anticipate precipitated silverchloride when SCET is used in humans. Though metallic silver dissolves in water to a concentration as low as 10 μg/l [41], the solubility of silverchloride in water is known to be 1 ppm [18]. However, in normal saline the maximum solubility of silver ions is assumed to be 32.5 μg/l, which is lower than the silver ion concentration provided by SCET. In fact, neither in normal saline (elution model) nor in PBS (continuously contaminated and mechanically ventilated model) did we see any cloudiness indicative of precipitated silverchloride. Furthermore, in our investigation all samples were filtered by a 0.2 μm membrane prior to determination of concentration of silver ions with no indication of precipitated silverchloride. This was the case even with concentrations as high as 550 μg/l. It was shown previously that minimal inhibitory concentrations of silver sulphadiazine in tissue were higher than the expected maximum solubility without showing precipitation [42]. In our

model *P. aeruginosa* and plexiglas might have accumulated silver ions thus inhibiting precipitation. We do not believe Ag^0 which might be masked by ASS measurements is the reason for no detectable precipitation. Recent own preliminary data showed effectiveness of SCET in 10^6 bacteria/ml which could not be reached if non-antimicrobial Ag^0 were present. Concerning SCET, proteins and mucous membranes located in the human oropharynx may lead to a certain complexation which lowers the probability of nonsoluble silverchloride [18,39]. One can speculate that a possibly reduced nucleation rate in human saliva or secretion acts in the same direction.

To conclude, SCET showed an inhibition of growth of *P. aeruginosa* in the continuously contaminated and mechanically ventilated oropharynx–larynx–lung model. In the oropharynx as well as in the lung there was a clinically significant reduction of more than 2 log. Further clinical studies on SCET have to address the issues of availability of silver ions in humans, biocompatibility and efficacy for other intensive care relevant bacteria. SCET may well be suited for reducing ventilator-associated pneumonia.

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