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Effects of dexmedetomidine on pharyngeal swallowing and esophageal motility—A double-blind randomized cross-over study in healthy volunteers

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Abstract

Background: Sedative agents increase the risk of pulmonary aspiration, where an intact swallowing function is an important defense mechanism. Dexmedetomidine is an α_2-adrenoceptor agonist widely used during procedural sedation due to beneficial properties with minimal respiratory effects. The effects of dexmedetomidine on pharyngeal swallowing and esophageal motility are not known in detail.

Methods: To determine the effects of dexmedetomidine on pharyngeal swallowing and esophageal motility, nineteen volunteers were included in this double-blinded, randomized placebo-controlled cross-over study. Study participants received target-controlled dexmedetomidine and placebo infusions. Recordings of pressure and impedance data were acquired using a manometry and impedance solid-state catheter. Data were analyzed from three bolus swallows series: baseline, during dexmedetomidine/placebo infusion at target plasma concentrations 0.6 ng ml^{-1} and 1.2 ng ml^{-1}. Subjective swallowing difficulties were also recorded.

Key Results: On pharyngeal swallowing, dexmedetomidine affected the upper esophageal sphincter with decreased pre- and post-swallow contractile pressures and an increase in residual pressure during swallow-related relaxation. On esophageal function, dexmedetomidine decreased contractile vigor of the proximal esophagus and increased velocity of the peristaltic contraction wave. Residual pressures during swallow-related esophagogastric junction (EGJ) relaxation decreased, as did basal EGJ resting pressure. The effects on the functional variables were not clearly dose-dependent, but mild subjective swallowing difficulties were more common at the higher dose level.

Conclusions and Inferences: Dexmedetomidine induces effects on pharyngeal swallowing and esophageal motility, which should be considered in clinical patient management and also when a sedative agent for procedural sedation or for manometric examination is to be chosen.

KEYWORDS
dexmedetomidine, esophageal motility, pulmonary aspiration, sedatives, swallowing function

1 | INTRODUCTION

During minor surgical procedures, procedural sedation is often preferred over general anesthesia because of advantages, for example, in terms of shorter recovery times and less postoperative nausea and vomiting. However, sedation is performed with an unprotected airway and the sedative agents used can impair laryngeal reflexes, esophageal sphincter, and swallowing function, leading to an increased risk of pulmonary aspiration.[1] To minimize the risk of gastric regurgitation and pulmonary aspiration, guidelines advocate pre-procedural fasting, monitoring of the depth of sedation and preparedness for airway management.[2] Depending on their pharmacodynamic and pharmacokinetic profiles, commonly used sedative agents such as propofol, opioids, and benzodiazepines have different effects on swallowing function and esophageal motility.[3–8]

In recent years, dexmedetomidine, a selective α_2-adrenoceptor agonist with sympatholytic, sedative, and analgesic properties combined with minimal respiratory effects and an easily aroused patient, has gained popularity as a sedative agent during minor surgical procedures and in the intensive care unit, in both intubated and non-intubated patients.[9,10] In a systematic review by Barends et al., comparing dexmedetomidine and midazolam for procedural sedation, dexmedetomidine provided more comfort during the procedure for both the patient and the clinician, with similar safety profiles, suggesting the possibility that the use of dexmedetomidine will continue to increase in the future.[11]

Different subtypes of α_2-adrenoceptors are variably expressed both in the CNS and in peripheral tissues, including the GI tract.[12] Despite their frequent use and the possible risk of pulmonary aspiration, the effects of dexmedetomidine and other α_2-adrenoceptor agonists on swallowing function in humans have not been extensively investigated. Our research identified only one study where Sanuki et al. examined swallowing reflexes with submental EMG electrodes under the influence of dexmedetomidine in healthy volunteers; the authors concluded that dexmedetomidine sedation was associated with a potential risk of aspiration due to depression of the swallowing reflex during elevation of the larynx.[13]

The present study aimed to evaluate the effects of dexmedetomidine on pharyngeal swallowing function and esophageal motility using a high-resolution impedance manometry catheter. We also examined whether sedation with dexmedetomidine was associated with subjective swallowing difficulties.

Key points

- Dexmedetomidine, a selective α2-adrenoceptor agonist, has gained widespread use as a sedative agent during procedural sedation.
- This randomized controlled trial is the first to investigate the effects of dexmedetomidine on human swallowing function.
- An intact swallowing function is an important defense mechanism to avoid pulmonary aspiration during sedation.
- Using the "Swallow Gateway" online platform to analyze manometry and impedance data, we demonstrated that dexmedetomidine affects pharyngeal swallowing as well as esophageal motility and EGJ pressures.

2 | MATERIALS AND METHODS

2.1 | Participants

With approval from the Central Ethics Review Board in Uppsala, Sweden (Dnr 2017/270), 20 healthy volunteers were recruited by advertisements at the local university. This double-blinded, randomized, and placebo-controlled cross-over study (ClinicalTrials.gov registration number NCT03390972) was conducted at the Department of Anesthesiology and Intensive Care, University Hospital in Örebro, Sweden. Informed consent was obtained after the participant candidate had received verbal and written information about the study. Each participant had a pre-study medical history assessment and physical examination including electrocardiography. The main inclusion criteria were age 18–40 years, body mass index (BMI) 18–30 kg/m^2, and willingness and ability to comply with the protocol for the duration of the trial. The exclusion criteria included current or past symptoms of pharyngo-esophageal dysfunction, cardio-pulmonary or neurological disease, known heart rhythm disorder, tendency to faint, medication that could affect the GI tract or the airways, allergy to study drug, smoking, pregnancy or breastfeeding, and participation in an ongoing medicinal clinical trial where follow-up was not completed. All participants received financial compensation for participation. Adverse events were recorded according to Good Clinical Practice guidelines.

2.2 | Interventions

In a cross-over design, the experiment was performed at two separate occasions for each participant, at least 7 days apart. The participants received an intravenous target-controlled infusion (TCI) of dexmedetomidine at the target plasma concentration of 0.6 ng ml^{-1}, followed by a higher target concentration of 1.2 ng ml^{-1} or a placebo infusion (physiological saline solution) in a randomized and balanced order (Figure 1). The target concentrations were chosen to reflect mild to moderate sedation (0.6 ng ml^{-1}) and moderate-to-deep sedation (1.2 ng ml^{-1}), that is, clinically relevant drug exposures.[14,15] The randomization list was prepared by the study statistician using SPSS. The participants as well as the assessor of the data were blinded

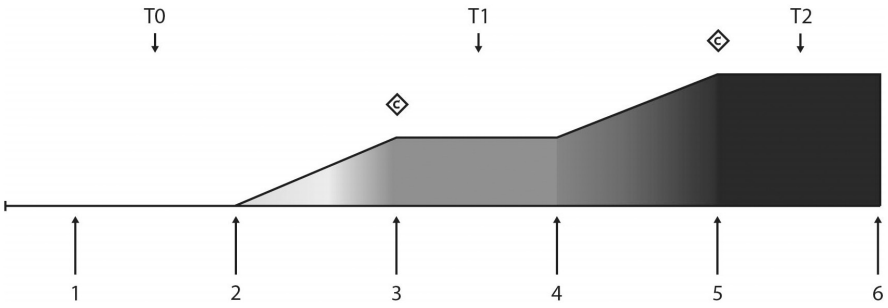

FIGURE 1 Study outline. 1; insertion of manometry/impedance catheter. T0; first swallow series. 2; Start of study medication (dexmedetomidine/placebo) target concentration 0.6 ng/ml. 3; Target concentration reached. T1; Second swallow series with study drug at 0.6 ng/ml. 4; Increase of target concentration to 1.2 ng/ml. 5; Target concentration reached. T2; Third swallow series with study drug at 1.2 ng/ml. 6; End of experiment. Diamonds with the letter C represent blood sampling for plasma concentration measurements

to which treatment was given. Fasting for at least 6 hours was required before the infusions. A Harvard 22 syringe pump (Harvard Apparatus, USA) and a portable computer running Stanpump software (by Steven L. Schafer, M.D., http://www.opentci.org/code/stanpump) were used for drug administration.

2.3 | High-resolution impedance manometry

A solid-state manometry and impedance catheter was used for collection of pressure and impedance data (Manoscan, Medtronic, Minneapolis, MN, USA). Details about the catheter are described elsewhere.[16] The catheter was calibrated in accordance with the manufacturer's specifications before insertion.

The catheter was inserted transnasally with the participants in the supine position with 30° elevation of the headboard. After correct positioning, with sensors recording from the pharynx to the stomach, the participants rested for 5 minutes to accommodate with the catheter. Baseline measurements were thereafter recorded without study drug (T0). A series of bolus swallows of five 10-ml aliquots of thin liquid were performed. The boluses were administered with a 20-ml syringe and consisted of a standardized conductive liquid bolus medium product containing 0.6% w/v of NaCl (SBM-kit; Trisco Foods Pty Ltd, Brisbane, Australia).[17] After the baseline measurements, the study drug infusion (dexmedetomidine or placebo) was started, and when the target concentration of 0.6 ng ml^{-1} had been reached, a second series of bolus swallows was performed (T1). Thereafter, the target concentration of the study drug was increased to 1.2 ng ml^{-1} and when this concentration was reached, the third and last swallowing series was performed (T2).

2.4 | Vital signs, sedation scales, and drug concentration measurements

During the entire experimental sessions, all participants were monitored with electrocardiography and recordings of non-invasive blood pressure, pulse oximetry, and end-tidal carbon dioxide ($ETCO_2$). To monitor depth of sedation, Bispectral Index (BIS) was used. Prior to each swallow series, the level of sedation was also rated using the Richmond Agitation-Sedation Scale (RASS), monitored by study personnel.[18] All participants were also asked to rate their level of sedation on a numerical rating scale (NRS) from 0 to 10, with 0 = fully awake to 10 = almost impossible to stay awake. Blood samples for determination of concentrations of dexmedetomidine in plasma were obtained at two occasions, when the target concentrations of 0.6 ng ml^{-1} and 1.2 ng ml^{-1} were reached.

2.5 | Subjective swallowing difficulties

After each swallowing series the participants were asked to grade eventual swallowing difficulties on a four-point scale from 1 to 4, where 1 = no difficulties, 2 = mild difficulties, 3 = moderate difficulties, and 4 = severe difficulties.

2.6 | Pressure-flow analysis

Recordings of pressure impedance data from the ManoScan system were displayed as pressure topography plots with embedded impedance recordings. The plots show the peristaltic wave and bolus flow movements. All recorded data were exported to the online semi-automated pressure-flow analysis portal (swallowgateway.com) where the recordings were analyzed to derive different swallow function variables.[4]

In the Swallow-Gateway portal, pharyngeal and esophageal regions of interest (ROI) were captured from the pressure topography plot and different space–time landmarks were selected as described in a previous article.[16] After these landmarks were correctly placed, an image was created, and a table of swallow properties was populated automatically. The analyzed pharyngeal and esophageal variables all represent different components of swallowing functions, such as bolus flow timing, intrabolus pressure, contractile vigor, bolus presence, and transluminal diameter (Table 1).

TABLE 1 Description of pharyngeal and esophageal metrics

	Unit	Description
Pharyngeal metrics		
Swallow Risk Index (SRI)		A measure of global function
UES maximum admittance (UES Max Adm)	ms	A measure of opening extent in the UES
UES integrated relaxation pressure (UES IRP)	mmHg	A measure of UES restriction
UES relaxation time (UES Open Time)	s	A measure of UES opening period
UES pre-swallow basal pressure (UES BP)	mmHg	A measure of UES regional weakness
Hypopharyngeal peak pressure (Peak P)	mmHg	A measure of hypopharyngeal regional weakness
UES post-relaxation peak pressure (UES Peak P)	mmHg	A measure of UES contractility
Hypopharyngeal bolus presence Time (BPT)	s	A measurement of oral control.
Distension to contraction latency (DCL)	s	A Measure of flow timing
Post-deglutitive UES contractile integral UESCI	mmHg*cm*s	A measure of UES contractility
Esophageal metrics		
Proximal esophageal contractile integral (PCI es)	mmHg*cm*s	A measure of proximal esophageal contractility
Distal esophageal contractile integral (DCI)	mmHg*cm*s	A measure of distal esophageal contractility
Distal contractile velocity (DCV)	cm/s	A measure of distal contraction velocity
Distal latency (DL)	s	A measure of time to contraction
EGJ 4 sec integrated relaxation pressure (IRP4s)	mmHg	A measure of EGJ obstruction
Distension pressure accommodation (DPA)	mmHg	A measure of flow resistance UES to T-Zone
Distension pressure compartmentalized transport (DPCT)	mmHg	A measure of flow resistance T-Zone to EGJ
Distension pressure emptying (DPE)	mmHg	A measure of flow resistance EGJ to diaphragm
Distal ramp pressure (RP)	mmHg/s	A measure of pressure change during lumen closure above EGJ
Swallow-distension latency (SDL)	s	A measure of bolus distension timing
Distension-contraction latency (DCL)	s	A measure of time from distention to contraction wave
Bolus presence time (BPTes)	s	A measure of bolus transport time to EGJ
Bolus flow time (BFT)	s	A measure of the bolus transit time across the EGJ

Abbreviations: EGJ, esophagogastric junction; T-Zone, Transition zone between striated and smooth musculature; UES, Upper esophageal sphincter.

2.7 | Statistical analysis

The number of study participants was estimated based on previous findings on effects of remifentanil, an ultrashort-acting μ-opioid receptor agonist, on pharyngeal swallowing.[16] From the observations of that study, the current sample size was calculated based on the pressure-flow variable distension-contraction latency (DCL), a key variable affected by remifentanil that describes the latency from bolus distension to pharyngeal contraction. Assuming a similar magnitude of effect on this outcome variable in the present study as in our previous study with remifentanil, and similar standard deviations, a sample size of 16 was calculated to have 80% power to detect similar mean differences when a paired t-test is used with a 5% two-sided significance level. The current study was planned to include 20 volunteers to compensate for possible drop-outs or technical difficulties. Power analysis was performed using Query Advisor version 6.0 (Statistical Solutions Ltd., Cork, Ireland).

A mean value of each pressure-flow analysis (PFA) variable was calculated from the five swallows of the 10 ml bolus volume swallowed in each series. Linear mixed models with random intercept and unstructured correlation for repeated measurements were used to evaluate the PFA outcome variables. Fixed factors were study treatment (dexmedetomidine/placebo), time (T0 baseline, T1 dexmedetomidine target concentration 0.6 $ng\,ml^{-1}$ or placebo, T2 dexmedetomidine target concentration 1.2 $ng\,ml^{-1}$ or placebo), and the treatment x time interaction, period (first/second) and sequence (dexmedetomidine first/placebo first). The vital parameter outcome variables were evaluated in the same manner: If any outcome variable showed a skewed distribution, the mixed model analysis was also performed with the data transformed on a $\log_{10}$ scale; these results are presented in the tables of the results section as a second p-value only if their statistical significance was different from that obtained with non-transformed data. Chi-squared test or Fischer's exact test when appropriate was used to compare NRS >= 3, RASS score changes and swallowing difficulties T1–T0 and T2–T1 between the dexmedetomidine and placebo treatments. Line plots showing crude means with 95% confidence intervals are used for illustrations. p-values <0.05 were regarded as statistically significant. All statistical computations were performed with IBM SPSS programs, version 27.

3 | RESULTS

Twenty healthy volunteers were recruited; one participant withdrew her consent because of discomfort of the manometry catheter at the first treatment session. Thus, 19 volunteers, 10 males and nine females, completed the study. Their mean age was 23.4 (SD ± 3.2) years and BMI 22.9 (SD ± 2.1) kg/m^2. The study was performed during January to June 2018. Some of the volunteers experienced discomfort of the catheter, but the drug intervention was well tolerated. Only three participants fulfilled one of the predefined criteria of adverse events; that is, a > 30% decrease in mean arterial pressure compared with baseline. These blood pressure reductions were not associated with subjective symptoms, and none of these participants reached a mean arterial pressure lower than 65 mmHg. No serious adverse events or suspected unexpected serious adverse reactions were recorded. Even though the participants were sedated, especially at the higher target concentration, they were easily aroused and could readily comply with the requirements of the protocol.

3.1 | Pharyngeal pressure-flow variables, dexmedetomidine vs. placebo

Detailed results for all pharyngeal variables are shown in Table 2. Three of the variables were significantly affected by dexmedetomidine at predicted target concentration 0.6 ng ml^{-1} compared with placebo: Upper Esophageal Sphincter (UES) integrated relaxation pressure (UES IRP) was increased with a mean difference of 1.5 mmHg (CI 95% 0.2 to 2.8). UES Pre-swallow basal pressure (UES BP) was reduced, with a mean difference of −20.9 mmHg (CI 95% −32.9 to −8.85) (Figure 2A). Post-Deglutitive UES Contractile Integral (UES CI) was reduced, with a mean reduction of −116 mmHg*s*cm (CI 95% −225 to −6.5) (Figure 2B). The UES IRP increase was augmented with increased plasma concentrations of dexmedetomidine, with a further mean difference of 1.9 mmHg(CI 95% 0.6 to 3.1) to 1.2 ng ml^{-1} (Table 2).

3.2 | Esophageal pressure-flow variables, dexmedetomidine vs. placebo

Esophageal variables that were significantly affected by dexmedetomidine at 0.6 ng ml^{-1} predicted dexmedetomidine concentration compared with placebo were: Proximal esophageal contractile Integral (PCI es), with a mean reduction of −283 mmHg*s*cm (CI 95% −337 to −166), and distal contractile velocity (DCV), with a mean increase of 0.7 cm/s (CI 95% 0.4 to 1.0). Effects on PCIes and DCV were augmented with increased plasma concentrations to 1.2 ng ml^{-1} with a further decrease of −56.2 mmHg*s*cm (CI 95% −112 to 0.0) and a velocity increase of 0.6 cm/s (CI 95% 0.1 to 1.1) (Table 2 and Figure 2C,D).

3.3 | Esophagogastric junction pressure-flow variables, dexmedetomidine vs. placebo

Esophagogastric junction (EGJ) variables that were significantly affected by dexmedetomidine at 0.6 ng ml^{-1} predicted dexmedetomidine concentration compared with placebo were: EGJ 4 sec integrated relaxation pressure (IRP 4 s), with a reduction of − 2.1 mmHg (CI 95% −3.8 to −0.6), bolus presence time (BPT) with a reduction of −1.7 s (CI 95% −3.0 to −0.3) (Table 2 and Figure 2E,F) and EGJ resting pressure (EGJ RP); decreased by −7.6 mmHg (CI 95% −13.3 to −1.9) (Table 2).

3.4 | Subjective swallowing difficulties

Some participants reported mild swallowing difficulties during the dexmedetomidine infusion, with a higher incidence (8/19) of subjective swallowing difficulties at 1.2 ng ml^{-1} target concentration compared with (4/19) at 0.6 ng ml^{-1} (Table 3).

3.5 | Vital signs, sedation scales, and dexmedetomidine concentrations in plasma

Circulatory parameters were significantly affected by dexmedetomidine compared with placebo with a dose-dependent reduction in both mean arterial blood pressure and heart rate. Respiratory parameters were mainly unaffected, with no difference in respiratory rate or $ETCO_2$ between dexmedetomidine and placebo, and a small yet statistically significant reduction in SaO_2 after dexmedetomidine compared with placebo. The sedation scales and BIS all showed significantly deeper sedation in a dose-dependent manner during the dexmedetomidine infusion compared with placebo (Table 3).

The mean measured concentrations of dexmedetomidine in plasma were slightly less than the target concentration of 0.6 ng ml^{-1} and slightly over the target concentration of 1.2 ng ml^{-1}, that is, 0.52 ng ml^{-1} (SD ±0.19) and 1.4 ng ml^{-1} (SD ±0.28), respectively (Figure 3).

4 | DISCUSSION

Several subtypes of adrenoceptors are expressed in the CNS, human upper airways, and GI tract. To our knowledge, the specific effects of α_2-adrenoceptor modulation on pharyngo-esophageal neuromuscular functions have not previously been investigated in human in vivo experiments. This study examined the effects of dexmedetomidine, a highly selective α_2-adrenoceptor agonist, on pharyngeal swallowing and esophageal motility in healthy volunteers. Two different target concentrations were used to establish whether the possible drug effects were dose-related.

TABLE 2 Effects of dexmedetomidine on pharyngeal and esophageal metrics compared with placebo

Condition	Baseline Dexmedetomidine	Baseline Placebo	Dexmedetomidine 0.6 ng/ml	Placebo	Dexmedetomidine 1.2 ng/ml	Placebo	Dexmedetomidine 0.6 ng/ml vs Placebo		Dexmedetomidine 0.6 to 1.2 ng/ml vs Placebo	
	T0		T1		T2		T1 vs T0		T2 vs T1	
Time	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Men diff (95% CI)	*p*	Men diff (95% CI)	*p*
Pharyngeal Metrics										
SRI	1.5 (0.9)	1.4 (0.6)	1.7 (1.0)	2.0 (1.2)	1.9 (1.1)	1.8 (1.2)	−0.0 (−0.5 to 0.5)	0.90	0.0 (−0.6 to 0.6)	0.96
UES Max Adm (mS)	4.2 (0.5)	4.4 (0.7)	4.1 (0.7)	4.1 (0.5)	4.0 (0.6)	4.2 (0.6)	−0.1 (−0.2 to 0.4)	0.52	−0.2 (−0.5 to 0.1)	0.25
IBP (mmHg)	4.4 (4.0)	5.2 (4.1)	5.2 (3.9)	5.5 (2.4)	6.5 (4.1)	5.5 (2.5)	0.6 (−1.2 to 2.4)	0.51	1.25 (−0.5 to 3.0)	0.16
0.25 s UES IRP (mmHg)	0.21 (3.2)	1.9 (2.8)	1.3 (2.7)	1.4 (2.3)	2.7 (2.5)	1.0 (2.5)	1.5 (0.2 to 2.8)	**0.025**	1.89 (0.6 to 3.1)	**0.004**
UES Open Time (s)	0.64 (0.05)	0.63 (0.05)	0.60 (0.05)	0.61 (0.07)	0.59 (0.04)	0.61 (0.05)	−0.010 (−0.04 to 0.01)	0.4	−0.005 (−0.03 to 0.02)	0.61
UES BP (mmHg)	87.7 (31.0)	85.0 (32.3)	54.4 (21.6)	72.6 (24.9)	50.8 (25.0)	67.0 (24.9)	−20.9 (−32.9 to −8.85)	**0.001**	1.96 (−8.78 to 12.7)	0.71
Peak P (mmHg)	147 (39)	152 (39)	138 (36)	140 (37)	139 (50)	130 (35)	3.8 (−9.8 to 17)	0.58	11.2 (−5.7 to 28)	0.19
UES Peak P (mmHg)	273 (68)	281 (82)	255 (85)	259 (65)	264 (123)	248 (57)	5.16 (−26 to 36)	0.74	19 (−14 to 53)	0.25
BPT (s)	0.60 (0.05)	0.59 (0.07)	0.57 (0.07)	0.57 (0.06)	0.59 (0.09)	0.57 (0.13)	−0.03 (−0.09 to 0.03)	0.92	0.012 (−0.04 to 0.06)	0.64
DCL (s)	0.52 (0.06)	0.52 (0.08)	0.50 (0.06)	0.50 (0.07)	0.48 (0.06)	0.50 (0.06)	−0,01 (−0.03 to 0.02)	0.49	−0.02 (−0.05 to 0.01)	0.16
UESCI (mmHg*s*cm)	650 (230)	642 (225)	434 (144)	542 (195)	430 (183)	506 (181)	−116 (−225 to −6.5)	**0.038**	32.0 (−39.1 to 103)	0.37
Esophageal Metrics										
PCI es (mmHg*s*cm)	404 (220)	373 (176)	156 (123)	376 (209)	90.6 (91.3)	367 (222)	−251 (−337 to −166)	**<0.001**	−56.2 (−112 to 0.0)	**0.005**
DCI (mmHg*s*cm)	1057 (745)	1085 (667)	1288 (697)	1183 (778)	971 (458)	1325 (876)	−326 (−683 to 29)	0.071	--459 (−744 to −175)	**0.002**
DCV (cm/s)	3.3 (0.5)	3.3 (0.4)	4.1 (0.6)	3.3 (0.4)	4.8 (1.1)	3.5 (0.6)	0.7 (0.4 to 1.0)	**<0.001**	0.6 (0.1 to 1.1)	**0.011**
DL (s)	8.5 (0.8)	9.1 (2.5)	7.4 (0.9)	8.6 (1.0)	6.8 (1.2)	8.4 (1.0)	−0.54 (−2.0 to −0.1)	0.29	−0.44 (−0.9 to 0.05)	0.08
IRP4s (mmHg)	8.3 (3.7)	7.2 (2.3)	6.2 (3.3)	7.3 (2.9)	5.7 (3.1)	7.3 (2.8)	−2.1 (−3.8 to −0.6)	**0.015**	−0.5 (−1.9 to 0.96)	0.49
DPA (mmHg)	2.7 (2.7)	4.6 (4.5)	2.6 (3.3)	3.5 (4.4)	2.5 (2.8)	2.8 (3.2)	0.92 (−0.7 to 2.6)	0.27	0.60 (−0.91 to 2.1)	0.43
DPCT (mmHg)	6.2 (2.6)	6.2 (3.2)	5.7 (2.8)	6.1 (2.8)	5.9 (1.9)	6.3 (2.4)	−0.28 (−1.6 to 1.1)	0.69	−0.02 (−1.0 to 0.9)	0.97
DPE (mmHg)	11.2 (3.3)	10.0 (3.2)	11.0 (3.4)	11.3 (2.6)	11.6 (2.1)	11.6 (2.1)	−1.6 (−3.5 to 0.37)	0.11	0.37 (−0.78 to −1.5)	0.52
RP (mmHg/s)	6.2 (2.7)	5.6 (4.9)	3.5 (2.1)	4.9 (2.2)	3.6 (1.6)	4.1 (1.9)	−0.96 (−3.6 to 1.7)	0.39	0.04 (−1.2 to 1.3)	0.95
SDL (s)	4.1 (1.2)	4.7 (2.2)	3.8 (0.45)	4.5 (0.90)	3.5 (0.68)	4.3 (0.91)	−0.14 (−1.3 to 1.1)	0.81	−0.13 (−0.65 to 0.39)	0.61
DCL (s)	4.3 (1.0)	4.5 (1.2)	3.6 (0.9)	4.1 (1.2)	3.3 (1.1)	4.1 (1.3)	−0.40 (−1.2 to 0.4)	0.31	−0.31 (−1.0 to 0.4)	0.38
BPT es (s)	9.3 (1.5)	9.6 (1.6)	7.2 (1.1)	9.2 (1.5)	6.6 (1.4)	9.3 (1.9)	−1.7 (−3.0 to −0.3)	**0.016**	−0.7 (−1.8 to 0.3)	0.17
BFT (s)	5.6 (1.7)	6.2 (1.6)	4.7 (1.2)	5.7 (1.2)	4.4 (1.5)	5.8 (1.6)	−0.4 (−1.5 to 0.7)	0.48	−0.4 (−1.4 to 0.6)	0.41
EGJRP (mmHg)	23.7 (10.1)	14.7 (7.2)	10.0 (5.2)	25.6 (10.5)	24.3 (8.4)	25.7 (10.7)	−7.6 (−13.3 to −1.9)	**0,01**	−6.2 (−10.2 to-2.2)	**0.003**

Note: Mean values and standard deviation of pharyngeal and esophageal metrics for each swallow series, T0 = baseline values without study drug, T1 = during administration of study drug at predicted target concentration 0.6 ng/ml, T2 = during administration of study drug at predicted target concentration 1.2 ng/ml. Mean differences (95% confidence interval) comparing study infusions were analyzed using mixed model. For explanations of abbreviations and metrics, see Table 1.

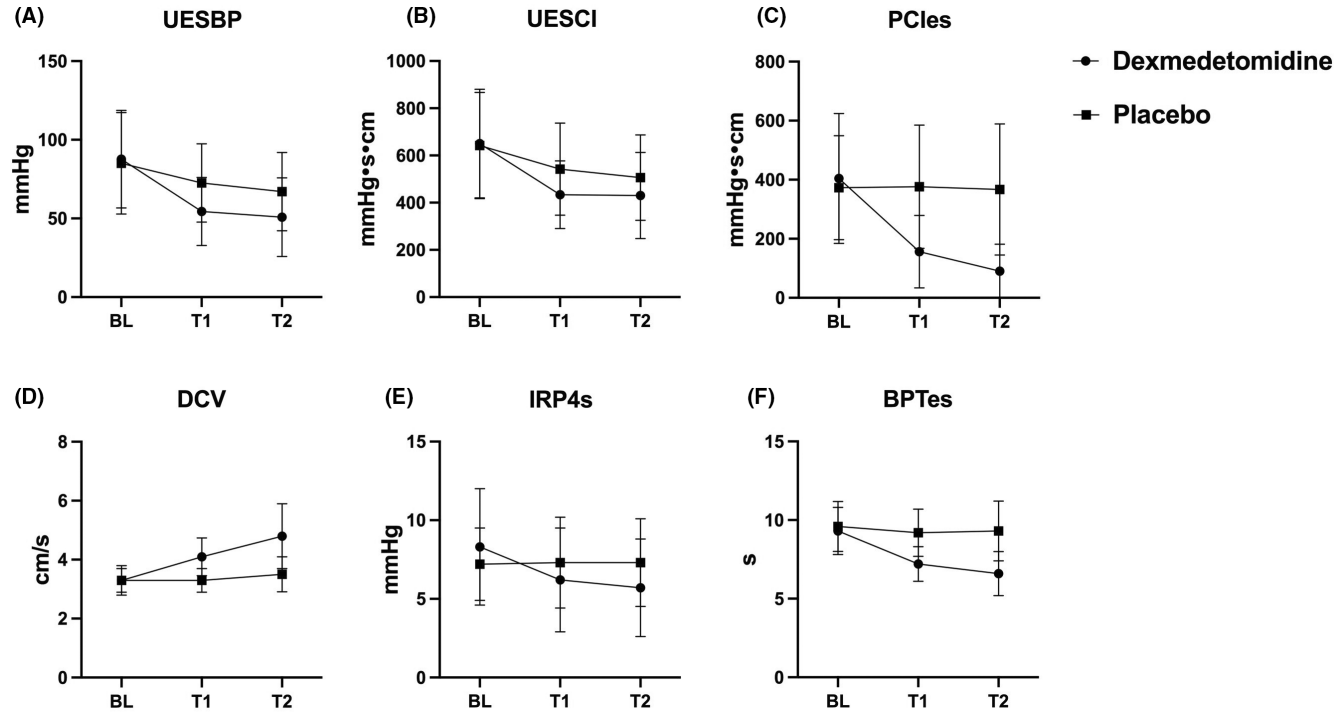

FIGURE 2 The effects of dexmedetomidine on pharyngeal and esophageal variables compared to placebo. Presented as mean line plots with 95% Confidence Interval error bars. BL= without study drug; T1= with study drug at predicted plasma concentration 0.6 ng/ml; T2= with study drug at predicted plasma concentration 1.2 ng/ml. UES BP = UES Pre-Swallow Basal Pressure, UESCI = Post-Deglutitive UES Contractile Integral, PCIes= Proximal Esophageal Contractile Integral, DCV = Distal Contractile Velocity, IRP4s = EGJ 4sec Integrated Relaxation Pressure, BPTes = Bolus Presence Time

The main observed effects of dexmedetomidine on pharyngeal swallowing were in relation to the upper sphincter function, leading to weaker pre- and post-swallow contractile pressures and an increase in residual pressure during swallow-related relaxation. Regarding esophageal function during deglutition, dexmedetomidine decreased contractile vigor of the proximal esophagus. In the distal esophagus, vigor appeared unaffected. However, the propagation velocity of the peristaltic contraction wave increased. The residual pressures during swallow-related EGJ relaxation decreased, as did the basal EGJ resting pressure. The observed changes in UES residual pressure, proximal contractility, and distal contractile velocity were augmented with increased plasma concentrations of dexmedetomidine. Other novel parameters defining luminal bolus distension timing, distension pressure, and distension opening during bolus transport were for the most part unaffected by dexmedetomidine.

Three different subtypes of α_2-adrenoceptors (subtypes A, B, and C) mediate the different and broad-ranging pharmacodynamic effects of dexmedetomidine.[12] These receptors are present in the CNS, in peripheral tissues and in the autonomic ganglia at presynaptic and postsynaptic sites. It is thus unsurprising that some effects of α_2-adrenoceptor activation by dexmedetomidine on pharyngeal, esophageal, and lower esophageal sphincter (LES) motor function were seen. In reporting of our findings, it is also important to differentiate between effects on striated and smooth muscle, which are discussed separately.

4.1 | Sedative effects on swallowing function

Reduced wakefulness has an effect on pharyngeal swallowing and esophageal motility.[19,20] Therefore, centrally acting sedatives also affect swallowing function. However, apart from the overall sedative effects, the different sedatives demonstrate a variety of effects depending on the mechanism of action. Drugs acting mainly on GABA receptors, like benzodiazepines and propofol, are thought to inhibit GABA-modulated neurons in the swallowing central pattern generator (CPG) in the lower brain stem with impairment of the swallow reflex.[21,22] Dexmedetomidine differs from these traditional sedatives that inhibit the excitatory reaction of the brain to stimuli; instead, dexmedetomidine acts on noncortical and subcortical structures with no impairment or disinhibition of cognitive function.[23]

4.2 | Pharynx and Proximal Esophagus

Regarding the depression of pre- and post-relaxation excitability of the UES, several studies have demonstrated that the tone of the UES high-pressure zone is highly variable and responsive to a range of factors[24]; UES pressure varies with the state of arousal,[20] is reduced during sleep,[19] increases during emotional stress,[25] and can be consciously controlled.[26] Pre- and/or post-swallow activation of UES as well as contraction of the proximal esophagus are

TABLE 3 Vital signs, swallow difficulties, and sedation scales

	Dex	Placebo	Dex 0.6 ng/ml	Placebo	Dex 1.2 ng/ml	Placebo	Dex 0.6 ng/ml vs. placebo		Dex 1.2 ng/ml vs. placebo		Dex 1.2 ng/ml vs. 0.6 ng/ml	
	T0	T0	T1	T1	T2	T2	T1 vs. T0		T2 vs. T0		T2 vs. T1	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean diff (95% CI)	*p*	Mean diff (95% CI)	*p*	Mean diff (95% CI)	*p*
MAP	100.0 (6.3)	99.3 (6.5)	84.8 (8.4)	98.0 (7.8)	78.6 (8.3)	96.6 (6.0)	−13.9 (−18.3 to −9.5)	**<0.001**	−18.8 (−23.5 to −14.0)	**<0.001**	−4.9 (−7.8 to −1.9)	**0.002**
HR	82.0 (13.4)	80.3 (11.9)	68.7 (10.3)	73.9 (10.7)	62.4 (7.6)	73.6 (9.2)	−7.0 (−10.8 to −3.3)	**0.001**	−12.9 (−14.3 to −11.6)	**<0.001**	−5.9 (−10.7 to −1.1)	**0.018**
RR	16.0 (2.6)	14.7 (2.7)	15.4 (2.8)	16.0 (2.1)	15.1 (2.7)	15.4 (2.7)	−1.9 (−3.9 to 0.0)	0.055	−1.6 (−3.9 to 0.7)	0.16	0.3 (−1.5 to 2.1)	0.72
SaO_2	97.9 (1.1)	98.1 (1.3)	96.4 (1.6)	98.0 (1.0)	96.6 (1.3)	98.0 (0.9)	−1.4 (−2.7 to −0.1)	**0.040**	−1.2 (−2.4 to −0.0)	**0.044**	0.2 (−0.4 to 0.8)	0.60
$EtCO_2$	5.2 (0.5)	5.0 (0.7)	5.5 (0.5)	5.2 (0.5)	5.7 (0.4)	5.2 (0.5)	0.1 (−0.2 to 0.4)	0.50	0.3 (−0.0 to 0.6)	0.082	0.2 (−0.1 to 0.4)	0.16
NRS	0.0 (0.0)	0.0 (0.0)	4.2 (2.6)	0.1 (0.4)	8.0 (1.2)	0.0 (0.0)	4.1 (3.0 to 5.2)	**<0.001**	8.0 (7.4 to 8.6)	**<0.001**	3.9 (2.8 to 4.9)	**<0.001**
NRS≥3, n (%)	0 (0%)	0 (0%)	12 (63%)	0 (0%)	19 (100%)	0 (0%)		**<0.001**		**<0.001**		**0.008**
RASS, n (%)								**<0.001**		**<0.001**		**<0.001**
−3	0	0	0	0	8 (42%)	0						
−2	0	0	1 (5%)	0	11 (58%)	0						
−1	0	0	11 (58%)	0	0	0						
0	19 (100%)	19 (100%)	7 (37%)	19 (100%)	0	19 (100%)						
Swallow difficulties								0.74		0.046		0.10
No difficulties	16 (84%)	17 (89%)	15 (79%)	18 (95%)	11 (58%)	18 (95%)						
Mild	3 (16%)	2 (11%)	4 (21%)	1 (5%)	8 (42%)	1 (5%)						
Moderate	0	0	0	0	0	0						
Severe	0	0	0	0	0	0						
BIS	96.9 (1.2)	95.9 (3.2)	91.2 (7.1)	96.8 (1.3)	73.1 (12.4)	96.9 (1.6)	−6.6 (−10.2 to −3.1)	**0.001**	−24.8 (−30.6 to −19.0)	**<0.001**	−18.2 (−24.1 to −12.2)	**<0.001**

Note: SD = standard deviation, T0 = baseline before dexmedetomidine or placebo, T1 = dexmedetomidine 0.6 ng/ml or placebo, T2 = dexmedetomidine 1.2 ng/ml or placebo. Mean differences (95% confidence interval) comparing study infusions were analyzed using mixed model. MAP = mean arterial pressure; HR = heart rate; RR = respiratory rate; SaO2 = oxygen saturation in percent measured by pulse oximetry; EtCO2 = end-tidal carbon dioxide in percent in exhaled gas; NRS = Numeric Rating Scale for sedation level; RASS = Richmond Agitation-Sedation Scale measuring the agitation or sedation level; BIS = Bispectral Index, monitoring depth of anesthesia. Fischer exact test was used to compare NRS >=3 and RASS score changes T1–T0, T2–T0, and T2–T1 between dexmedetomidine and placebo groups.

The bold values are statistically significant.

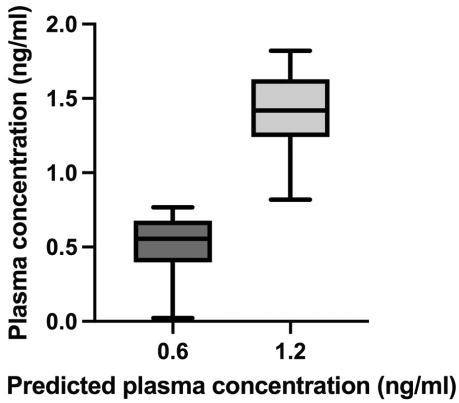

FIGURE 3 Box plot of measured plasma concentrations at predicted target plasma concentration 0.6ng/ml and 1.2 ng/ml

modulated in response to the volume and/or viscosity of the swallowed bolus.[17] As α_2-adrenoceptors are abundant in both peripheral and central parts of the nervous system, the anatomical origin of the effects of dexmedetomidine seen on pharyngeal swallowing is uncertain. In a study on brainstem-spinal cord, preparations of the rat where the effects of different noradrenergic drugs on coordination of swallowing and breathing were examined. Stimulation of the supralaryngeal nerve showed that clonidine, an α_2-adrenoceptor agonist, significantly shortened the prolongation of expiratory duration induced by swallowing activity, whereas the α_2-antagonist yohimbine had an opposite effect.[27] This finding suggests that some of the pharyngeal effects seen with dexmedetomidine could be due to α_2-adrenoceptor modulation of neurons in the ventrolateral medulla.

Dexmedetomidine exposure could also depress the corticobulbar and peripheral mechanisms regulating the sequential activation of motor pools that drive pharyngo-esophageal segment contraction. We speculate that these effects may alter the activity or coordination of muscles that govern hyolaryngeal elevation and provide extrinsic traction, important for UES relaxation, and opening. Such an effect could explain the paradoxical finding of a small but significant increase in the residual UES relaxation pressure during dexmedetomidine exposure. However, further studies, potentially utilizing submental muscle electromyography, would be required. Interestingly, contractility of the hypopharynx, which demonstrates a highly stereotypical response with little or no change in response to bolus conditions, was unaffected by dexmedetomidine.[17] Muscle contractility was thus not globally impaired, making peripheral presynaptic and/or direct muscle effects an unlikely explanation for the observed changes.

Our observations, combined with α_2-agonist effects in animal models, suggest that the observed effects on the CNS-controlled functions may be a result of inhibitory effects of α_2-adrenoceptor stimulation of neurons in the brainstem, or secondary to the somnolescent effects evoked by dexmedetomidine mediated through activation of central pre- and postsynaptic α_2-adrenoceptors in the locus coeruleus.[28]

4.3 | Distal Esophagus and Esophagogastric Junction

Results of animal experiments have suggested that α-adrenoceptor mediated pathways may play some role in modulating esophageal smooth muscle motility, but mixed effects have been reported.[29–31]

Our findings in healthy human participants demonstrated no significant effect of dexmedetomidine on distal contractile vigor in the esophagus. However, the peristaltic contraction was found to propagate more rapidly (faster DCV) in a dose-dependent fashion. Distal latency (DL), by contrast, was not significantly affected. A pattern of rapid contraction in the absence of change in DL may be explained by a prolonged latency of the proximal, but not distal, part of the smooth muscle esophagus.

Investigations of the lower esophageal sphincter (LES), which receives both parasympathetic and sympathetic inputs, suggest that α-adrenoceptor mediated mechanisms may here play a far greater role than in the esophageal body.

A major source of innervation of the smooth muscle comprising the lower esophagus and LES is the dorsal motor nucleus of the vagus (DMV), which receives more noradrenergic terminals than any other medullary nucleus.[32–35] In whole-cell recordings of DMV neurons in the rat, pretreatment with α_2-agonists and α_2-antagonists mimicked or antagonized the inhibitory effects of norepinephrine, respectively, suggesting that depolarization by norepinephrine is mediated by α_1-adrenoceptors, while norepinephrine-induced hyperpolarization would be mediated by α_2-adrenoceptors.

In the current study, α_2–adrenoceptor activation was associated with decreases in both resting and relaxation pressures recorded at the EGJ. This confirms the results from a study by Turan et al. where effects of propofol and dexmedetomidine on LES pressure were investigated. They found that at equal depth of sedation both propofol and dexmedetomidine similarly reduced LES pressure, however, with preserved gastroesophageal pressure gradient.[36] The reduction in LES tone seen with dexmedetomidine could have different explanations. As in other segments of the GI tract, dexmedetomidine might inhibit smooth muscle function by reducing acetylcholine release from cholinergic motor neurons via activation of presynaptic α_2-adrenoceptors located on cholinergic nerve terminals. Dexmedetomidine, similarly to propofol, is also a potent activator of nitric oxide synthase and increases endogenous nitric oxide production, which in turn may decrease LES pressure.[37,38]

In this study, dexmedetomidine was administered at two different target concentrations using a TCI system. The measured plasma concentrations of dexmedetomidine were quite close to the targeted. The two different target concentrations were chosen to reflect a light-to-moderate, and a moderate-to-deep level of sedation, respectively.[14,15] Evaluation with sedation scales and BIS demonstrated that desired levels of sedation were indeed achieved. The volunteers were more deeply sedated during the higher target concentration, and if the effects of dexmedetomidine are related to reduced wakefulness, one could argue that more

prominent effects, in a dose-dependent manner, would be seen with higher target concentrations. This was encountered in subjective swallowing difficulties, but not in all functional variables. However, one of the main characteristics of dexmedetomidine sedation is the property of arousability.[39] When the participants were asked to perform swallows, they were easily aroused even at the higher dexmedetomidine dose level, which could also influence the effects on swallowing function and esophageal motility even at higher doses.

During procedural sedation, it is of great importance to select a sedative drug suitable for both the individual patient and for the planned procedure. Dexmedetomidine is considered to be particularly suitable for procedural sedation because of minimal respiratory impairment and a cooperative patient. However, in risk management, it is important to understand that all sedatives seem to affect swallowing function, a function associated with pulmonary aspiration, where dexmedetomidine is no exemption.[40] It is also important to be aware of the possibility that if sedation is used during esophageal manometry, the sedative agent employed can affect the results of the examination. Esophageal manometry for the assessment of esophageal motility in dysphagia patients is preferably done without sedation. However, the transnasal catheter placement required for the manometric procedure is unpleasant for many patients. Light sedation is therefore sometimes used if the patient is otherwise unable to undergo the examination. Since the most unpleasant part is the insertion of the catheter, we recommend the use of a short-acting drug whose possible effects have waned off at the start of the examination. Propofol and remifentanil both exhibit these properties, where propofol is more favorable due to less specific effects on swallowing function. Dexmedetomidine should be used with caution due to considerable risk of residual effects because of its slower elimination.

4.4 | Strengths and Limitations

This is the first study examining the effects of dexmedetomidine on swallowing function and esophageal motility. The study was conducted as a randomized placebo-controlled trial, minimizing the risk of biased results. Furthermore, dexmedetomidine was administered as a target-controlled infusion and the actual plasma concentrations were verified.

The observed effects of dexmedetomidine on swallowing function may have been influenced by the drug's unique property of arousability, where the performance of swallowing on demand temporarily increases during the testing.

In the study only liquid boluses were assessed, examination with thick or semisolid boluses might have added valuable information. The use of thickener might have changed the perception of eventual dysphagia symptoms and even altered the results since viscous boluses have been shown to decrease UES relaxation time, UES basal pressure, and flow timing metrics, with increased UES opening extent.[17]

Swallowing difficulties were evaluated on a numerical scale that only provides subjective information. Pharyngeal sensation testing might have added more objective information.

The inclusion criteria were narrow, with a young and healthy study population. A homogenous study population reduces the risk of confounders when examining the effects of dexmedetomidine on the human swallow physiology. On the contrary, it could be argued that, since swallowing function declines with age, more profound effects might have been seen if we included older participants.[34] Another limitation of the study was that the time course of reversal of the drug effects was not evaluated; this was not technically feasible in the current experimental setting as the manometry catheter read-out starts to show significant drift after extended recording.

5 | CONCLUSIONS

Dexmedetomidine, like other sedatives, induces effects on pharyngeal swallowing and esophageal motility, which should be considered in clinical patient management and also when a sedative agent for procedural sedation or for manometric examination is to be chosen.

AUTHOR CONTRIBUTIONS

P.C. and J.S. conceived and designed research and performed experiments. P.C., T.O., A.M., H.S., M.S., and J.S. analyzed data and interpreted results of experiments. P.C. prepared figures and drafted manuscript. P.C., T.O., A.M., H.S., M.S., and J.S. edited and revised manuscript and approved the final version of the manuscript.

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DISCLOSURES

T.O. holds a noncommercialized US Patent (13/823072) relevant to the analysis technology used in the study. M.S. has contract research relationships with Orion Corporation (Espoo, Finland), AC Immune SA (Lausanne, Switzerland), Alzinova Ab (Gothenburg, Sweden), Biogen (Cambridge, MA, USA), Dr. Falk Pharma (Freiburg, Germany), Novartis (Basel, Switzerland), Novo Nordisk (Copenhagen, Denmark), and Provention Bio (Red Bank, NJ, USA); Dr. Mika Scheinin has also received speaker's fees from Pharma Industry Finland (Helsinki, Finland). None of the other authors has any conflicts of interest, financial, or otherwise, to disclose.

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