The tooth of time

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CHAPTER 4

Intranasal dexmedetomidine in elderly subjects with or without beta blockade: a randomised double-blind single-ascending-dose cohort study

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ABSTRACT

Background

The aim of this double blind, placebo-controlled, single ascending dose study was to determine the safety and tolerability of intranasal dexmedetomidine in the elderly.

Methods

We randomly assigned 48 patients ≥65 years of age to receive single doses intranasal dexmedetomidine or placebo (5 : 1 ratio) in 4 dose cohorts. The doses received by the sequential cohorts were 0.5, 1.0, 1.5 and 2.0 μg.kg^{-1}. Each dose cohort comprised two groups of 6 subjects: a group of subjects using β-blockers and one group not taking β-blockers. Vital parameters and sedation depth (MOAA/S, BIS) were measured for two hours after administration. Blood samples were taken to determine dexmedetomidine plasma concentrations.

Results

One subject (1.0 μg.kg^{-1}) had acute hypotension requiring ephedrine. Systolic blood pressure decreased more than 30% in 15 of 40 subjects (37.5%) receiving dexmedetomidine, lasting longer than 5 minutes in 11 subjects (27.5%). Mean arterial pressure decreased more than 30% (longer than 5 minutes) in 10%,20%,50% and 30% of subjects receiving dosages of 0.5, 1.0, 1.5 and 2.0 μg.kg^{-1} respectively, irrespective of β-blocker use. Heart rate decreased 10% -26%. MOAA/S-score ≤3 occurred in 18 (45%) subjects. 8 (20%) subjects receiving dexmedetomidine showed no signs of sedation. Tmax was 70 minutes. Cmax was between 0.15 ng ml^{-1} (0.5 μg.kg^{-1})and 0.46 ng.ml^{-1} (2.0 μg.kg^{-1}).

Conclusions

Intranasal dexmedetomidine in elderly subjects had a sedative effect but caused a high incidence of profound and sustained hypotension. The technique is unsuitable for routine clinical use.

4.1 Introduction

Intranasal administration of dexmedetomidine has been found to be safe and efficacious for the sedation of healthy adults and children.[97-100] Intranasal sedative administration has several benefits, one of which is that there is no need for IV access in order to achieve anxiolysis, and so this route can be used to provide a comfortable and well-tolerated method of sedation for children, phobic patients or those who are unable to cooperate due to an impaired cognitive function.

When sedating vulnerable elderly patients, health care providers must take into account the possible effects of the age-related physiological changes such as decline of renal and hepatic function and change in body composition, which can alter the pharmacokinetic profile of a drug in the elderly patient.[101] Furthermore, when procedural sedation of vulnerable, elderly patients in a nursing home is proposed, the safety profile of the drug in question must be firmly established.

To our knowledge intranasal administration of dexmedetomidine has not yet been studied in the elderly. No prior knowledge of the safety of intranasal dexmedetomidine in the elderly is available. Our hypothesis was that a single dose of intranasal dexmedetomidine can be administered to elderly people safely with respect to hemodynamic changes, irrespective of the concurrent use of β-blockers. Therefore, we performed a double blind, placebo controlled single ascending dose study to investigate the safety, tolerability and the sedative properties of four intranasal doses of dexmedetomidine in elderly subjects. Many elderly patients take β-blockers which might aggravate the cardiovascular effects of dexmedetomidine. We therefore included in each dose cohort equal numbers of patients taking β-blockers and patients not taking β-blockers.

4.2 Methods

4.2.1 Study management and registration

This study was performed at the University Medical Center Groningen, the Netherlands, in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice and the applicable regulatory requirements. Approval of the responsible ethics committee was received (NL55716.042.15) and all subjects provided written informed consent. The study was registered in the Dutch Trial Register (NTR5513)

4.2.2 Study execution

This was a study with a double blind and placebo controlled, single ascending dose design. We studied 4 doses of intranasally administered dexmedetomidine. The doses received by the sequential cohorts were 0.5, 1.0, 1.5 and 2.0 μg.kg^{-1}. In young adults and children dosages of 1.0 and 1.5 μg.kg^{-1} have shown to be effective.[97-100] Given the fact that elderly adults might plausibly be more susceptible to these doses the first cohort received a smaller dose: 0.5 μg.kg^{-1}. For completeness, and in case the elderly were less

susceptible, we included a larger dose of 2.0 μg.kg^{-1}. Each dose cohort consisted of 12 subjects, six using β-blockers and six not using β-blockers. Subjects within each dose cohort were randomized in a 5:1 ratio to receive either dexmedetomidine or placebo (normal saline 0.9%) respectively. Randomization was performed by the hospital pharmacy using an online randomization program (www.randomization.com, accessed on February 3rd 2016). The anesthesiologist, sedation practitioner and the subjects were blinded to both the randomization and the study drugs. Dexmedetomidine was provided by the hospital pharmacy in ampoules in blinded packages. Dexmedetomidine (Dexdor, Orion corporation, Espoo, Finland) in 2 ml ampoules (100 μg.ml^{-1}) was used for subjects randomized to the dexmedetomidine group. Normal saline 0,9% prepared in 2 ml blinded ampoules was used as placebo. The ampoules were drawn up into a 2ml syringe by a nurse not involved in the study and labeled by this nurse with a coded, blind study label from the same package.
Eligible subjects were elderly patients scheduled to undergo surgery under general anaesthesia. Inclusion criteria were: age ≥ 65 years, BMI ≥ 17.5 and ≤ 30.5 kg.m^{-2}, a total body weight >50 kg at screening and check-in, American Society of Anesthesiologists (ASA) Physical Status 1 or 2 and a Modified Mallampati Score I or II. Exclusion criteria were: contraindications for the use of dexmedetomidine[102], history or presence of significant disease (ASA >2), or significant cardiovascular disease risk factors, significant coronary artery disease, or any known genetic predisposition to cardiac arrhythmia (including long QT-syndrome), psychiatric disease, history of any illness or medication use that might confound the results of the study or pose an additional risk to the patient by their participation in the study, surgery within the past 90 days prior to dosing judged to be clinically relevant, history of febrile illness within 5 days prior to dosing, history or presence of alcoholism or drug abuse within the past 2 years, hypersensitivity or idiosyncratic reaction to components of dexmedetomidine, placebo components, or to compounds related to the study medications, single 12-lead ECG demonstrating QTcF interval >450 ms at screening or patient refusal.

On the day of the surgery subjects were transferred to a quiet room with low ambient light 2 hours before the planned starting time of their surgery. Subjects were monitored constantly during the entire study period. Emergency equipment and drugs were immediately available to treat hypotension, hypertension or other symptoms of cardiovascular or ventilatory compromise. Monitoring of vital signs was started before the start of the study: a 3-lead ECG, non-invasive blood pressure measurements and pulse oximetry were used to monitor vital signs. Additionally a BIS-monitor (BIS VISTA™monitor,Medtronic, Dublin, Ireland) was used and end-tidal CO_2 was measured by combined oral-nasal capnography (Smart CapnoLine®, Oridion Medical Ltd., Jerusalem, Israel). Prior to dexmedetomidine administration intravenous access was established and a baseline blood sample was collected from the intravenous cannula. Data from the vital signs monitor recording the physiological data were automatically recorded in the digital patient Data Management System CS-EZIS-Chipsoft (ChipSoft Elektronisch

Zorg Informatie Systeem, ChipSoft BV, Amsterdam, The Netherlands) at 15 seconds intervals. To avoid bias from blood pressure elevation induced by pre-operative anxiety we compared the blood pressure on arrival with the pre-operatively measured blood pressure. The lower of the two was used as baseline. Additionally the investigators used the time-logged CS-EZIS system (Chipsoft BV, Amsterdam, The Netherlands) to record the Modified Observers Assessment of Alertness and Sedation Score (MOAA/S) as well as clinical events and findings relevant to the study. Subjects were treated by an anesthesiologist or a registered Sedation Practitioner under indirect supervision of an anesthesiologist.

Dexmedetomidine or placebo was administered intranasally via a MAD atomizer (LMA® MAD Nasal™ Intranasal Mucosal Atomization Device, Teleflex Medical, Westmeath, Ireland). The volume in the syringe was adjusted to obtain the correct dose, depending on the dose cohort the subject had been assigned to. Volumes larger than 1 ml were distributed evenly over both nares so as not the exceed the recommended maximum volume of 1 ml per nares. Previous studies have used volumes in excess of 1 ml per nares but have divided these between both nostrils to minimize swallowing.[103, 104] Subjects were lying in the bed in a semi-recumbent position (45º angle) with the head tilted backwards during the administration. After administration the subject was asked to remain in his bed and not to engage in activities or spontaneous speech except for the required responses to MOAA/S scoring. ECG, SpO_2, end-tidal-CO_2 and BIS monitoring was performed continuously. Blood pressure was measured at 2.5 minute intervals for the first 45 minutes and at 5 minute intervals thereafter. MOAA/S was scored at 5 minute intervals. Venous blood samples were taken at baseline and 10, 15, 20, 30, 45 and 90 minutes after the administration of the study drug. Five milliliters of blood was drawn and discarded prior the sampling. Measurements were continued for a minimum of 90 minutes and a maximum of 120 minutes. Thereafter patient care was handed over to the anesthetic team responsible for the anesthesia during surgery, ending the study period.

Because the aim of the study was to investigate the safety of intranasally administered dexmedetomidine in the elderly a safety check was incorporated in the study design. Subjects were sequentially assigned to ascending dose cohorts. After each cohort was completed, a safety committee (comprising CB, MS and AA) met and applied a priori stopping criteria (Table 4-1) to determine if it was safe to proceed to the next dose. When 2 or more subjects in a dose cohort from either the group of subjects using β-blockers or the group not using β-blockers met the stopping criteria the inclusion would be terminated for that group.

Table 4-1 Stopping Criteria

Hemodynamic	Hypotension: systolic, diastolic or mean arterial blood pressure >30% below baseline with signs of hypoperfusion for more than 5 minutes or needing escape medication
	Hypertension (systolic blood pressure > 180mmHg; diastolic blood pressure >110 mmHg) for more than 5 minutes
	Bradycardia (heart rate <40 bpm for more than 5 minutes with signs of circulatory inadequacy)
	QTcF change from baseline >100 ms or total QTcF of >500 msec
Respiratory	Oxygen saturation <90% not resolved by simple verbal or light tactile stimulation
Sedative	Sustained MOAA/S score of ≤1 for ≥5 consecutive minutes.
Miscellaneous	Any clinically significant adverse events that the Sponsor and PI consider a safety concern
	Any serious adverse events which are considered by the PI as related to study drug

4.2.3 Statistical analysis

The design of this study was similar to that of 'first-in-man' type single ascending dose studies.

The primary endpoints were the number of subjects experiencing a decrease in systolic, diastolic or mean arterial blood pressure >30% below baseline for more than 5 minutes; the number of subjects per dose cohort experiencing bradycardia (heart rate below 40 beats per minute) for more than 1 minute and the maximum change from baseline in heart rate.

The secondary endpoints were the maximum change from baseline in systolic, diastolic or mean arterial blood pressure in 2.5 to 5 minute intervals per dose cohort, the time of peak plasma level of dexmedetomidine (Tmax), peak plasma level dexmedetomidine (Cmax), the mean change in sedation depth over time per dose cohort and the number of subjects per dose cohort reaching the stopping criteria.

There were no prior data available to inform a formal sample size calculation. We therefore pragmatically chose the sample size based on previous experience with similar studies of safety, efficacy, pharmacodynamics and pharmacokinetics of anesthetic drugs. For the primary outcomes simple descriptive statistics were used to summarize the findings. Differences in proportions between groups were tested using the Chi-square test. We constructed a linear mixed model for the change of mean arterial pressure over time. Initial factors in this model were: age, sex, the interactions between β-blocker-usage and time, and the interaction of the use of other antihypertensives and time. Stepwise removal of non-significant factors ($p>0.05$) was used to construct the final model. In each step the factor with the highest p-value was removed. In the final model only factors with p-values <0.05 remained. Univariate analysis was used to investigate the effects of dexmedetomidine dosages on heart rate and decrease in BIS. Statistical analyses were done in IBM SPSS Statistics, Version 23.0.0.3 (IBM, Armonk, New York, USA).

4.3 Results

Between March 2016 and July 2017 163 patients were eligible for inclusion based on a preliminary screening and the planning of their surgery, which had to allow for all study procedures to take place before the planned start of the surgery. Figure 4-1 shows a CONSORT diagram of the inclusion process and the reasons for exclusion. The characteristics of the included subjects and the use of β-blockers in group BB are summarized in Table 4-2. No subjects dropped out of the study during the study execution. One subject's scheduled surgery was brought forward unexpectedly which prevented us from taking the last blood sample at 90 minutes. The maximum recommended volume for intranasal administration (1ml per nares) was not exceeded in any subject. 27 subjects used additional antihypertensive medication. There was no significant difference between the different dose groups and the placebo group in the proportions of subjects using diuretics ($p=0.101$), ACE-inhibitors ($p=0.804$), calcium channel blockers ($p=0.923$) or ATII-inhibitors ($p=0.171$). Furthermore: the proportion of subjects using additional antihypertensive medication did not differ between the groups using β-blockers and the group not using β-blockers ($p=0.56$).

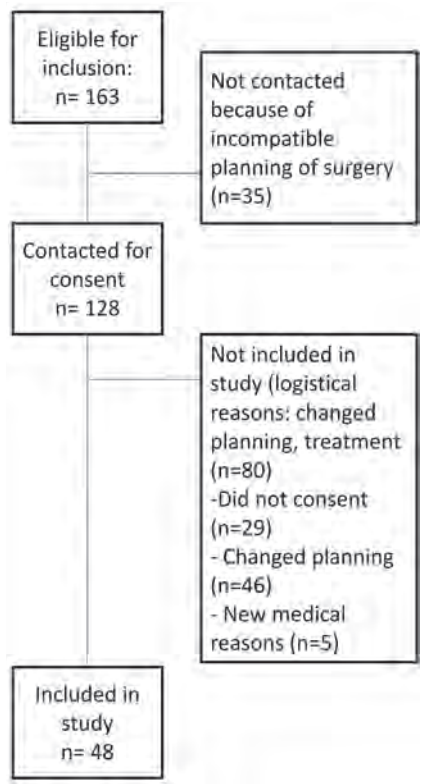

Figure 4-1 CONSORT diagram of inclusion process

Table 4-2 Demographics of the study population

	All	DEX	PBO
Total number of subjects	48	40	8
Sex (male/female) (n/n (%))	25/23 (52%/48%)	22/18 (55%/45%)	3/13 (38%/62%)
Age (Mean (SD) [range])	71.0 (4.9) [65-83]	71.0 (5.0) [65-83]	71.1 (4.4) [65-78]
ASA 1 (n(%))	6 (17.5%)	4 (10%)	2 (25%)
ASA 2 (n (%))	42 (87.5%)	36 (90%)	6 (75%)
Weight (kg, mean, SD)	78.1 (12.2)	79.3 (12.2)	72.2 (10.4)
Height (cm, mean, SD)	171 (9)	172 (9)	168 (7)
BMI (mean, SD)	26.5 (3.0)	26.7 (2.8)	25.5 (3.3)
Subjects using antihypertensive medication other than β-blockers	27	23 (57.5%)	4 (50%)
β-blockers use:	average dose ($mg.day^{-1}$ and range)	% of subjects (n)	
Metoprolol	78.85 (25-200)	54.2 (13)	
Bisoprolol	3.33 (2.5-7.5)	25 (6)	
Nebivolol	5 (5)	8.3 (2)	
Carvedilol	25 (25)	4.2 (1)	
Propranolol	10 (10)	4.2 (1)	
Sotalol	80 (80)	4.2 (1)	

DEX: dexmedetomidine; PBO: Placebo

4.3.1 Subjects meeting the Stopping Criteria

One subject (in the 1.0 $\mu g.kg^{-1}$ dose cohort) met two of the defined stopping criteria. The initial 73 minutes after dexmedetomidine administration were uneventful. Thereafter he suddenly experienced symptomatic hypotension, bradycardia, and severe nausea and dizziness. This was managed with administration of ephedrine (5 mg bolus iv), a rapid 500 ml bolus of Ringers Lactate solution and nursing in Trendelenburg position. Thereafter the bradycardia, hypotension and complaints resolved quickly and did not return. No other stopping criteria were met by any of the subjects, and therefore we continued including subjects into all dose cohorts.

4.3.2 Hemodynamic safety: hypotension, bradycardia and hypertension

Heart rate and blood pressure had a tendency to decrease over time. Table 4-3 presents the number of subjects with hypotension, hypotension lasting >5 min, hypotension requiring an intervention and the mean percentages decrease and time to nadir for systolic blood pressure, mean arterial pressure (MAP) and heart rate.

Table 4-3 Haemodynamic effects of dexmedetomidine and placebo

Dose cohort ($\mu g.kg^{-1}$)	**0.5** (n=10)	**1.0** (n=10)	**1.5** (n=10)	**2.0** (n=10)	**Placebo** (n=8)
Number of subjects experiencing: n (BB/NB) (per dose cohort)					
MAP decrease >30%	1 (0/1)	5 (4/1)	6 (3/3)	7 (3/4)	0
- Lasting longer than 5 min	1 (0/1)	2 (2/0)	5 (3/2)	3 (2/1)	0
- Requiring an intervention	0	1 (1/0)	1 (0/1)	1 (1/0)	0
Maximum percentage decrease per dose cohort (mean % (SD)) and time to nadir					
Heart rate	16.2 (9.2)	21.7 (7.9)	24.9 (10.0)	16.9 (9.1)	12.9 (6.2)
Time to nadir (min)	62	64	60	64	23
Systolic arterial blood pressure	19.1 (10.3)	27.9 (12.2)	28.3 (11.3)	33.1 (8.8)	9.3 (7.9)
Mean arterial blood pressure	19.8 (11.6)	28.0 (11.6)$^{\$}$	31.3 (11.5)$^{\$}$	34. 3 (6.4)$^{\$}$	11.5 (6.5)
Diastolic arterial blood pressure	19.2 (12.3)	29.5 (10.1)	33.8 (13.4)	34.1 (5.1)	19.1 (12.3)
Time to nadir MAP (min)	75	68	65	80	39

BB: n subjects taking β-blockers; NB: n subjects not taking β-blockers; MAP: mean arterial pressure. $: significantly different from placebo.

4.3.2.1 *Hypotension*

37.5% (n=15) of subjects who received dexmedetomidine experienced a decrease in systolic blood pressure of more than 30% from baseline, and in 27.5% (n=11) of subjects this lasted for longer than 5 minutes. 47.5% of subjects (n=19) who received dexmedetomidine had a decrease of their mean arterial pressure of more than 30% from the baseline, and in 27.5% (n=11) this lasted for more than 5 minutes. (Table 4-3) None of these subjects (except for the subject described above) had clinical signs of hypoperfusion. No subjects in the placebo group had a decrease in blood pressure of more than 30% from baseline.

A single dose of ephedrine (5mg) was administered intravenously to three subjects. This number includes the above mentioned subject (see: Subjects meeting the Stopping Criteria) and two additional subjects in whom ephedrine administration was deemed prudent because both had a history of cerebrovascular accidents and showed persistent declines of their blood pressure of >30% from baseline. The two latter subjects had no complaints nor any clinical signs of hypoperfusion and thus did not meet the formal stopping criteria.

4.3.2.2 *Bradycardia*

Symptomatic bradycardia was observed in only one subject as described above in the paragraph Subjects meeting the stopping criteria. No other subjects experienced bradycardia.

4.3.3 Respiratory safety

Respiration and arterial oxygen saturation remained relatively unaffected. Only one subject experienced a SpO_2 below 90% for more than 5 minutes but this resolved after verbal stimulation. Four subjects displayed some snoring with short decreases of arterial oxygen saturation. These desaturations were benign and self-limiting.

Figures Figure 4-2 to Figure 4-6 plot the time course for all individual subjects for heart rate (Figure 4-2), systolic blood pressure (Figure 4-3), mean arterial pressure (Figure 4-4), diastolic blood pressure (Figure 4-5) and pulse oximetry (Figure 4-6).

4.3.4 Secondary outcomes

The maximum percentage change in systolic blood pressure, mean arterial pressure and heart rate are summarized in Table 4-3. In the final linear mixed effects model only dexmedetomidine dose (F (5, 8.614)=63.906; p<0.001) was a significant factor in the decrease in MAP. β-blocker exposure, use of other antihypertensives, sex and age were not significant factors. The mean difference in maximum MAP decrease between subjects receiving placebo and those receiving 0.5 $\mu g.kg^{-1}$ of dexmedetomidine was not significant. For higher doses this difference was larger and significant (p≤0.001), (Table 4-2). Subjects who received dexmedetomidine also had a significantly larger decrease in

heart rate (p=0.03) than those who received placebo, with no significant effect from the use of β-blockers (p=0.89). The mean (SD) time to the nadir of mean arterial pressure of all subjects in the dexmedetomidine groups was 73 (20) minutes (72 (18) minutes for group BB and 72 (20) minutes for group NB)

4.3.4.1 *Sedative properties*

All subjects were lucid (MOAA/S 5) and able to respond adequately to MOAA/S-scoring at the start of the study period. BIS values could not be determined for 4 subjects due to a technical failure. Subjects receiving dexmedetomidine were significantly more sedated (as measured by BIS) than subjects receiving placebo (p=0.01). The mean (SD) time to the lowest BIS values was 65 (22) minutes (β-blocker group: 65 (22) and non β-blocker group: 59 (45)) One subject in the placebo group reached a MOAA/S score of 3; the BIS value at that point in time was 87. One subject (dose cohort 1.5 $\mu g.kg^{-1}$) reached a BIS of 16 with a suppression ratio of 22, 35 minutes after dexmedetomidine administration. The MOAA/S-score obtained 45 seconds later was 4 (BIS value at that time was 37).

The lowest MOAA/S scores reached by subjects, the time to lowest BIS values and lowest MOAA/S scores, and the times to peak measured dexmedetomidine concentrations per cohort are summarized in Table 4-4 for the different dose cohorts. All subjects remained rousable at all times, although, when most sedated, six subjects required “shake and shout” stimuli. The dose of dexmedetomidine correlated significantly with the maximum decrease in BIS as well as the lowest MOAA/S-score. (Spearman’s Rho: -0,43; p=0.003 and -0.633; p<0.001 respectively). Eight (20%) of the subjects in the dexmedetomidine groups did not display any clinical signs of sedation. Five of these subjects were in the lowest dose cohort of 0.5 $\mu g.kg^{-1}$. The three other subjects were in dose cohorts BB15, NB10 and NB20 respectively. Minimum BIS values for these subjects ranged from 72 to 91.

Figure 4-7 plots the time course for all individual subjects for Bispectral Index.

Table 4-4 : Cmax dexmedetomidine ; Tmax; maximum percentage decrease in BIS and time to lowest BIS in minutes ; lowest MOAA/S score reached by (n)-subjects

Dose Cohort		**0.5** (n=10)	**1.0** (n=10)	**1.5** (n=10)	**2.0** (n=10)	**Placebo** (n=8)
Cmax (ng.ml^{-1})		0.15 (0.03)	0.26 (0.05)	0.42 (0.13)	0.46 (0.13)	0
Tmax: (min)		81	78	63	57	
%-decrease BIS (mean (SD))		9.9 (9.9)	29.8 (10.9)	41.7 (17.8)	31.4 (13.4)	22.6(16.7)
Time to nadir (min)		55	61	65	75	53
Lowest MOAA/S score (number of subjects)						
Dose cohort		**0.5**	**1.0**	**1.5**	**2.0**	**Placebo**
MOAA/S-score	5	5	1	1	1	5
	4	4	7	2	1	2
	3	1	2	6	3	1
	2	0	0	1	5	0
	1	0	0	0	0	0
	0	0	0	0	0	0

Cmax: maximal plasma concentration of dexmedetomidine; Tmax time to highest plasma concentration of dexmedetomidine; BIS: BiSpectral Index; MOAA/S: Modified Observer's' Assessment of Alertness and Sedation

4.3.4.2 Plasma dexmedetomidine concentrations

Peak plasma levels (Cmax) per cohort are listed in Table 4-4. Tmax (mean (SD)) was 70 (26) minutes . There was no significant difference in Tmax between subjects taking β-blockers and subjects not taking β-blockers: 66 minutes (BB) and 71 minutes (NB) respectively (p=0.39).

4.3.4.3 Tolerability

All subjects tolerated the administration of dexmedetomidine or placebo well: no subjects experienced discomfort from the intranasal administration. Three subjects complained of a dry mouth, and three other subjects experienced mild nausea but did not vomit or require anti-emetics. All subjects had uneventful procedures under general anesthesia after participation.

4.4 Discussion

In this study of the safety and sedative properties of intranasal dexmedetomidine in elderly subjects, we found that while the three highest doses had sedative properties, they caused a significant decrease in blood pressure in a large proportion of the subjects. Although only one subject experienced clinical signs of hypoperfusion, the degree to which systolic blood pressure and mean arterial blood pressure were affected in a high percentage

of elderly subjects is a matter of concern. Furthermore it was deemed prudent by the anesthesiologist to administer ephedrine to two other subjects because the prolonged decline in blood pressure was thought to present a risk to their health.

We studied the use of intranasal dexmedetomidine with the intention to assess its safety and suitability for use in procedural sedation of the growing group of vulnerable, elderly patients. Previous studies have shown that dexmedetomidine appears safe when used in younger adults. The dosages used in the current study were selected from within the range of dosages that have been shown to produce minimal to moderate sedation in adults without causing significant hypotension.[98, 99, 105, 106] The incidence of hypotension in the current study is notably different, however, from the results of these previous studies of the effects of intranasal dexmedetomidine in younger adults.[98, 99, 105, 106] In the study by Zhang et al., the maximum mean decreases in systolic blood pressure was 9.0% and Nooh et al. reported no decreases of systolic blood pressure of more than 20%.[98, 99] In the current study, dosages needed to induce minimal or moderate sedation (1.0-2.0 μg.kg^{-1}) caused a change in systolic blood pressure of more than 20% in all three dose cohorts and a decrease of the MAP of more than 30% in a high percentage of the subjects. Decreases in blood pressure of the magnitude we have found, have been associated with an increased risk of perioperative stroke and renal and myocardial damage.[107, 108]

In each dose cohort we included equal numbers of subjects taking or not taking β-blockers. Elderly people frequently use β-blockers[109] and these drugs could plausibly amplify the hemodynamic effects of dexmedetomidine administration. Our data do not support this as the incidence of hypotension and bradycardia did not differ between the subjects taking β-blockers and subjects not taking β-blockers and the mean decreases in MAP and heart rate were not significantly determined by the use of β-blockers. In common with the general elderly population, a large proportion of subjects in our study were taking other antihypertensive medication at the time of the study. The proportions of subjects using additional antihypertensive medication did not differ significantly for subjects taking β-blockers and those not taking β-blockers. Further studies will be needed to determine whether other antihypertensive medications amplify the hypotensive effects of dexmedetomidine.

It took more than 60 minutes to reach the maximum sedative effect. This duration may limit the usefulness of intranasal dexmedetomidine for procedural sedation. Furthermore, although the time of onset of clinical effect and the time to maximum clinical effect in our study are comparable to those found in a study in younger adults, the maximum attained sedation depth was markedly different.[106] In the current study only 45% of the subjects receiving dosages of 1.0 μg.kg^{-1} and 1.5 μg.kg^{-1} attained a MOAAS-score of 3 or lower while, in the study involving younger adults 75% and 92% of the subjects attained a sedation level of MOAA/S of ≤3 after the same respective doses.[106] Moreover, although the BIS and sedation scores in our study suggest a moderate level of sedation in some subjects, we observed that the stimulation associated with MOAA/S-scores brought almost all subjects back to a lucid state for a short period of time. This well-known property of dexmedetomidine is probably the result of the fact that the sedative

effect of dexmedetomidine primarily seems to arise from actions on the natural sleep pathway.[110] The extent and duration of this arousal, accompanied by increases in BIS values, was recently quantified.[43] This does, however, give rise to doubts as to whether it will be useful for the procedural sedation of patients without cognitive coping strategies such as elderly patients suffering from major neurocognitive disorders who may need deeper, more sustained sedation. Yuen raised similar concerns about younger adults, stating :"... whether these doses will produce clinical sedation in anxious patients facing surgery or other painful procedures will need to be evaluated".[106] Deeper sedation with dexmedetomidine will require higher dosages, which will result in more profound hemodynamic effects.[43, 45]

With regard to pharmacokinetic parameters, the results in our elderly population are comparable to those found in a study of intranasal dexmedetomidine in younger adults where a median Cmax of 0.28 ng.ml^{-1} after 1.0 µg.kg^{-1} was found whereas for the same dose we found a median Cmax of 0.26 ng.ml^{-1}.[111] In the current study the onset of clinical effect of intranasal dexmedetomidine was at 20-30 minutes after administration. This is in accordance with the findings from previous studies in younger adults.[99, 111] Finally the Tmax in the current study for 1.0 µg.kg^{-1} is comparable to the Tmax found by Li et al. (78 vs 75 minutes).[111]

The current study has some noteworthy strengths and limitations. We performed a double blinded placebo controlled study to minimize the risk of bias. This is reflected by the differences observed between the dexmedetomidine group and the placebo group in the measurements of both the hemodynamic parameters and the observed sedation depth. The latter parameter was obtained using the MOAA/S-score by a blinded observer, but also objectively by using a BIS-monitor. In spite of the limited sample sizes we were able to determine significant differences in effect size between dexmedetomidine and placebo for mean arterial pressure and BIS with sufficient power (99% and 97% respectively). The power for the test of the difference in maximum heart rate was lower (73%) owing to the limited sample size and the limited effect size.

A limitation of our study is the fact that with intranasal administration of any liquid drug formulation, a variable proportion of the administered volume might reach the pharynx and be swallowed, thus changing the drug absorption rate and possibly the maximum attainable plasma concentration. This swallowing of intranasally delivered drugs is dependent on many factors, one of which is the administered volume. [112] In the current study the maximum recommended volume per nares of 1 ml was not exceeded for any subject.[113] We cannot, however, rule out the possibility that an unknown quantity of dexmedetomidine was not absorbed by the nasal mucosa of some subjects but was swallowed and thus delivered orally or absorbed by the pharyngeal mucosa. The bioavailability after oral administration of dexmedetomidine is only 16%[114] while after intranasal administration it has been found to be 40.6% (95% CI 34.7 - 54.4%).[111] We administered a fixed concentration of dexmedetomidine so that different subjects

received different volumes of drug, but have not controlled for the administered volume. These uncertainties prevent us from making more detailed comparative or predictive analyses of the pharmacokinetic profile and the pharmacodynamic effects we have found. In the case that some of our subjects swallowed significant amounts of the administered dose, resulting in reduced bioavailability, this would have altered the time to peak effect and would plausibly have underestimated the hemodynamic and sedative effects of the doses of dexmedetomidine in this age group. Additional studies that are able to control for volume, and preferably also for swallowing, are needed.

The data from the current study cannot be used to generate a full pharmacokinetic profile of dexmedetomidine after intranasal administration in the elderly. The subjects in this study received dexmedetomidine in the preoperative phase. Since the subsequent induction of general anaesthesia would have influenced many important parameters determining the pharmacokinetic profile we refrained from blood sampling in later stages and therefore limited ourselves to the pharmacokinetic measurements we have presented. The results do suggest however, that the differences in hemodynamic and sedative effects found in our population and those found in younger adults in previous studies, are more likely to be due to pharmacodynamic than pharmacokinetic differences.

4.5 Conclusion

In conclusion, in this study intranasal dexmedetomidine produced minimal to moderate sedation in elderly subjects but caused a high incidence of hypotension, irrespective of β-blocker use. The technique is unsuitable for routine clinical use.

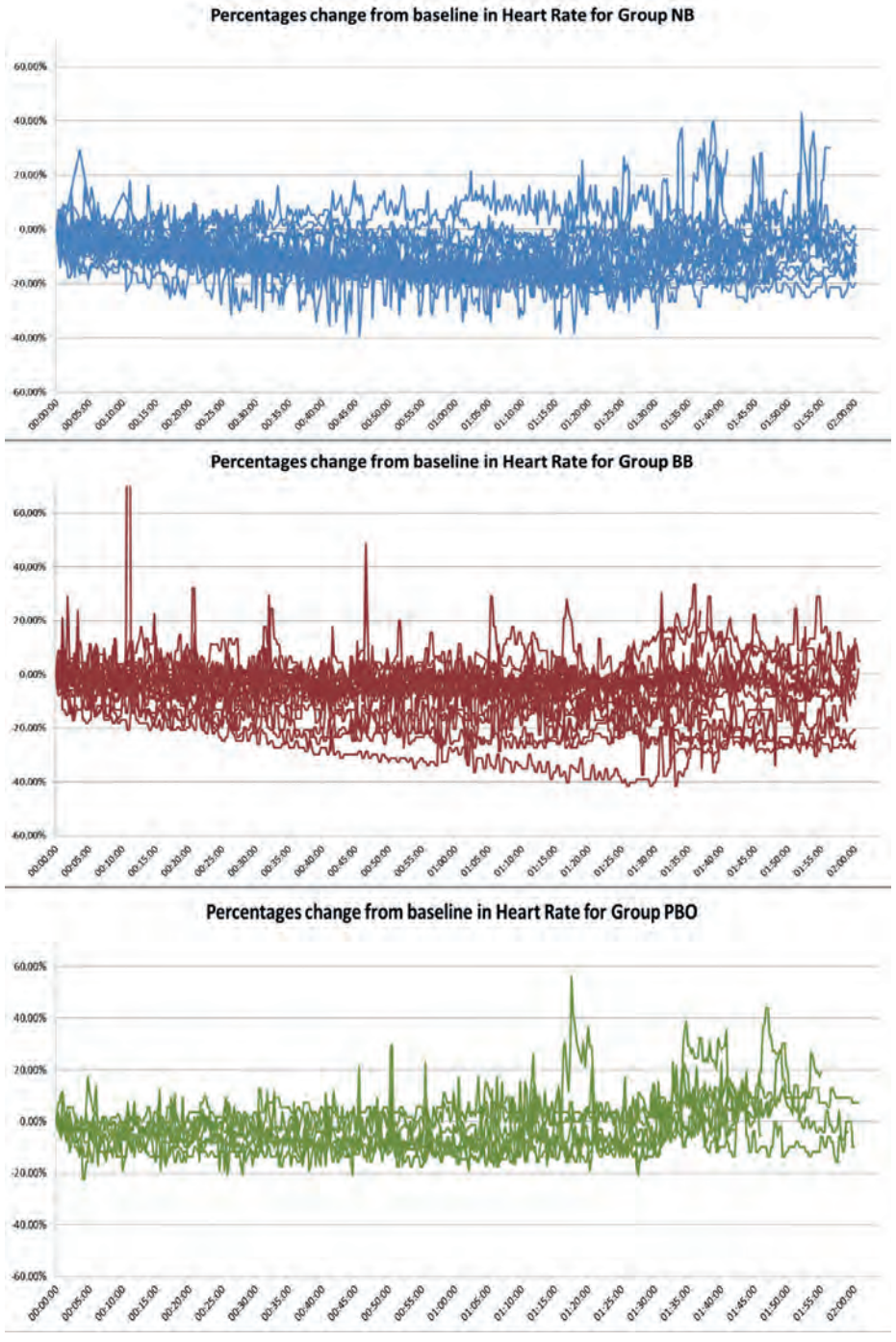

Figure 4-2 Percentage change in heart rate

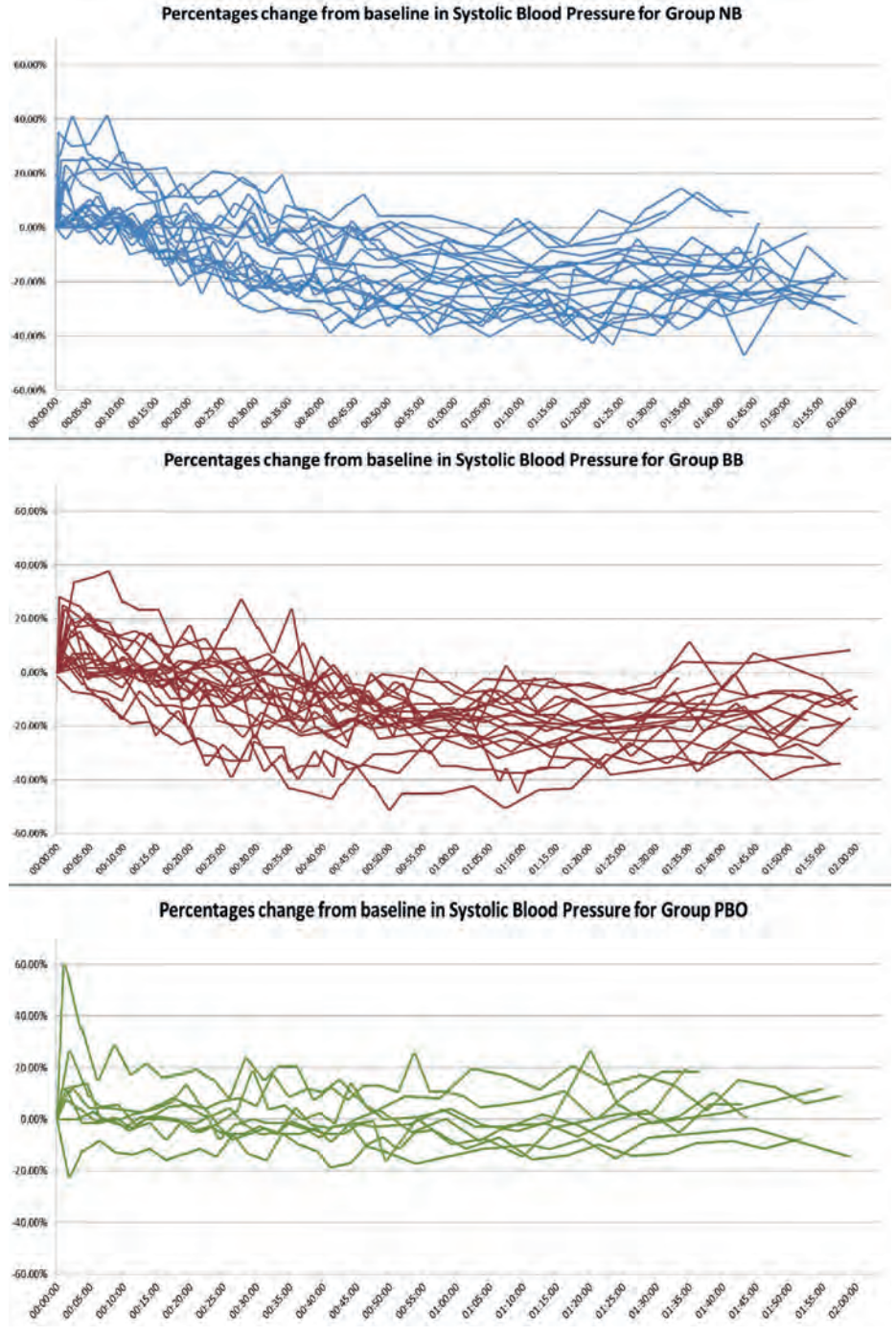

Figure 4-3 Percentage change in systolic blood pressure

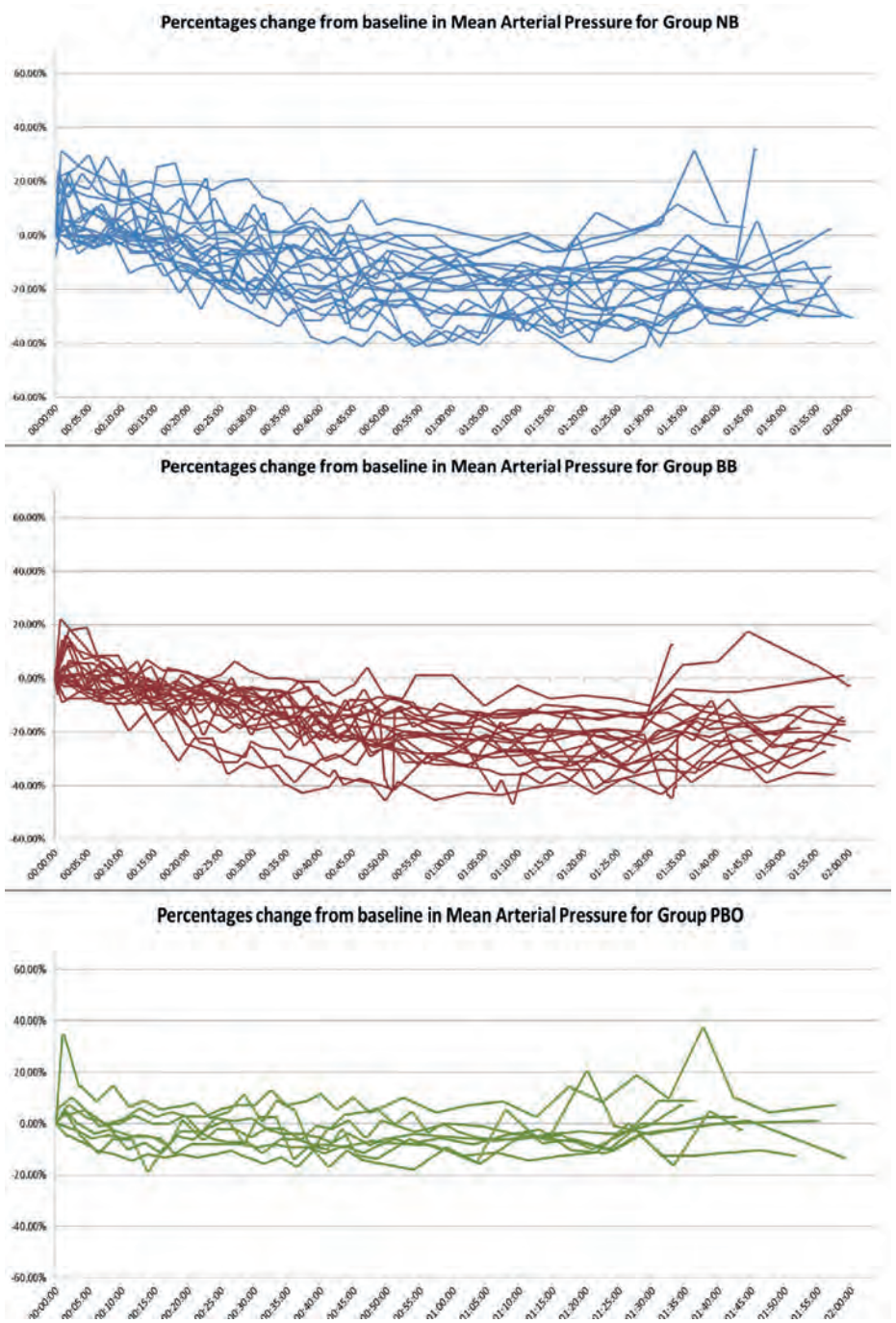

Figure 4-4 Percentage change in mean arterial pressure

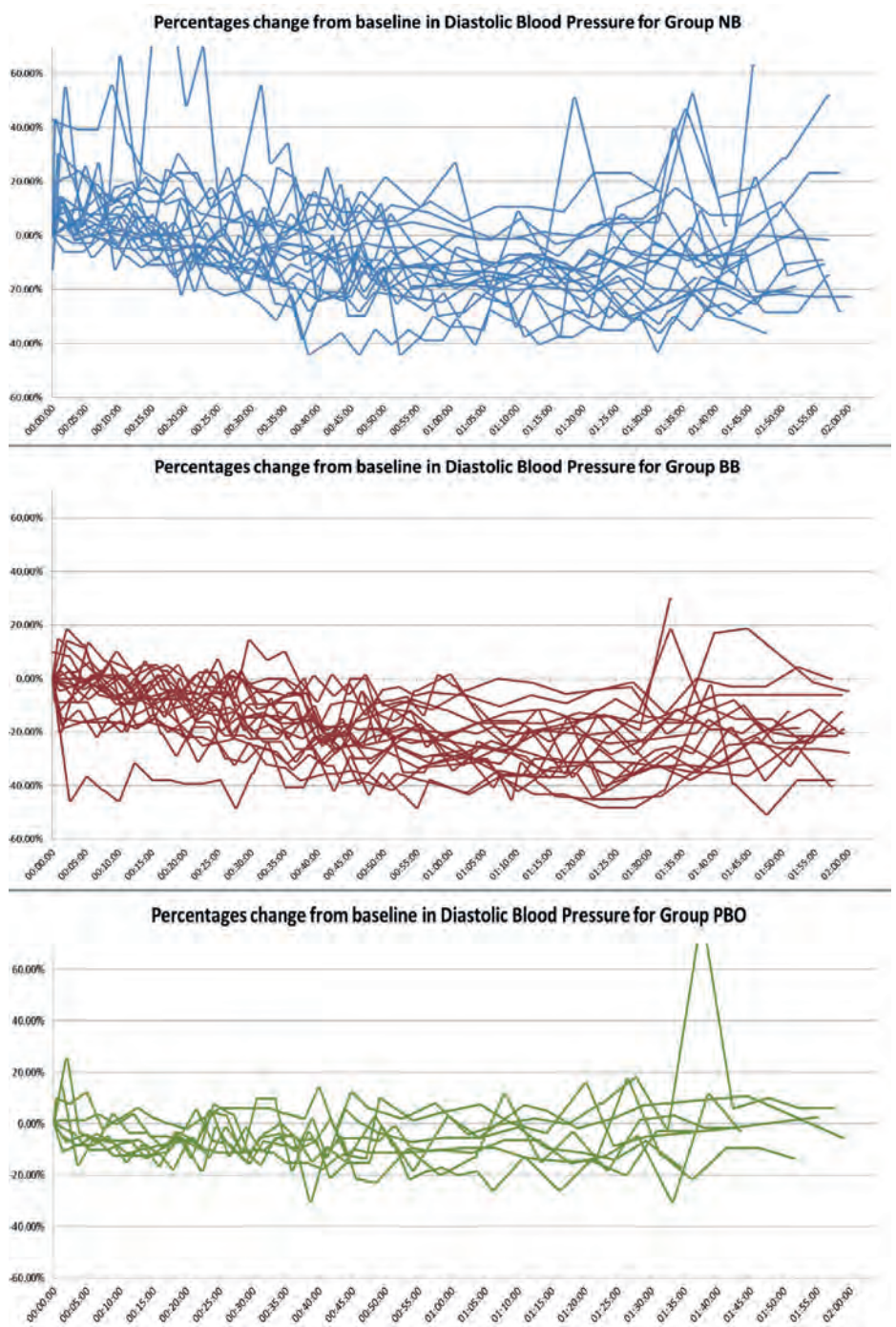

Figure 4-5 Percentage change in diastolic blood pressure

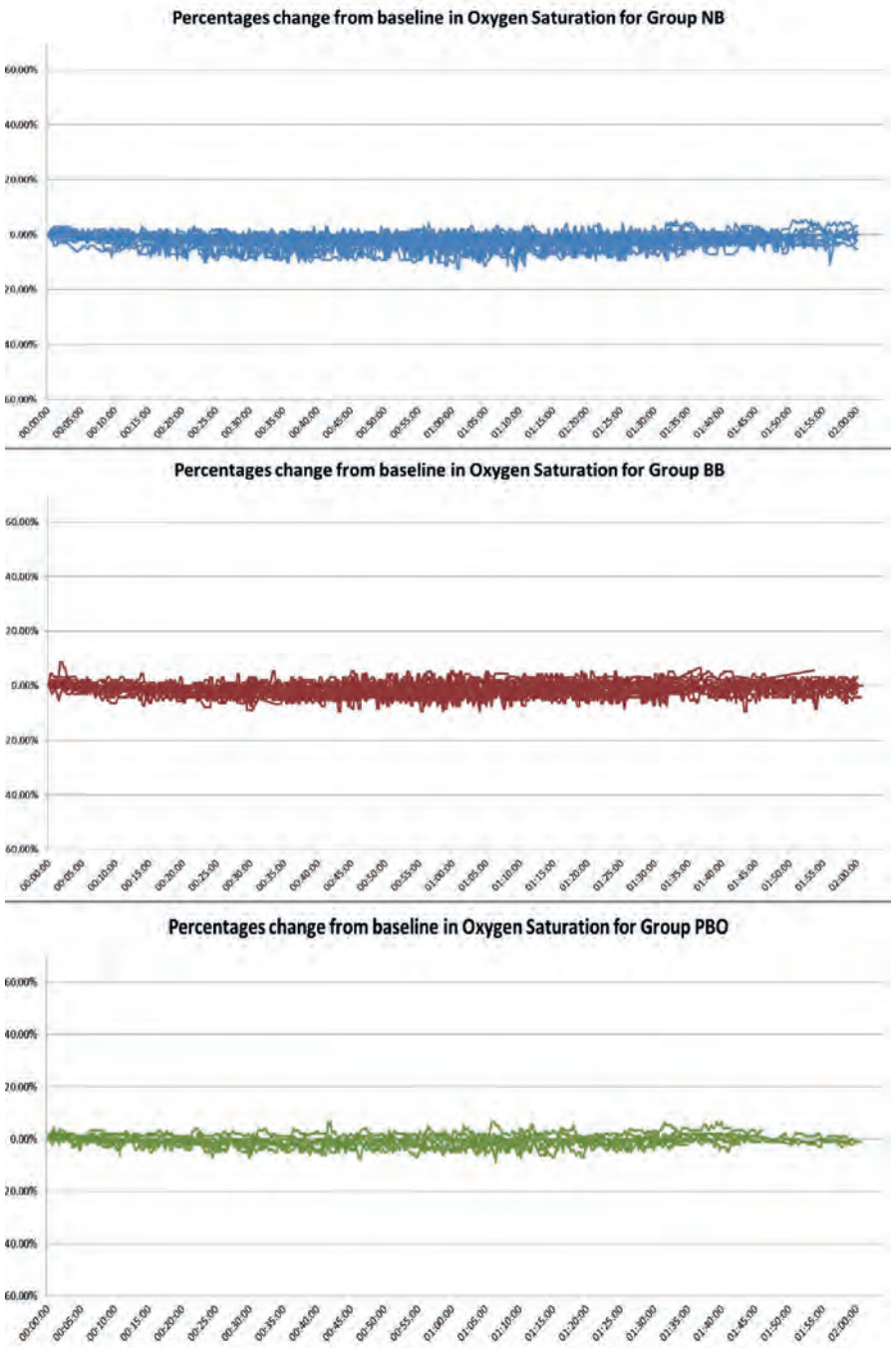

Figure 4-6 Percentage change in oxygen saturation

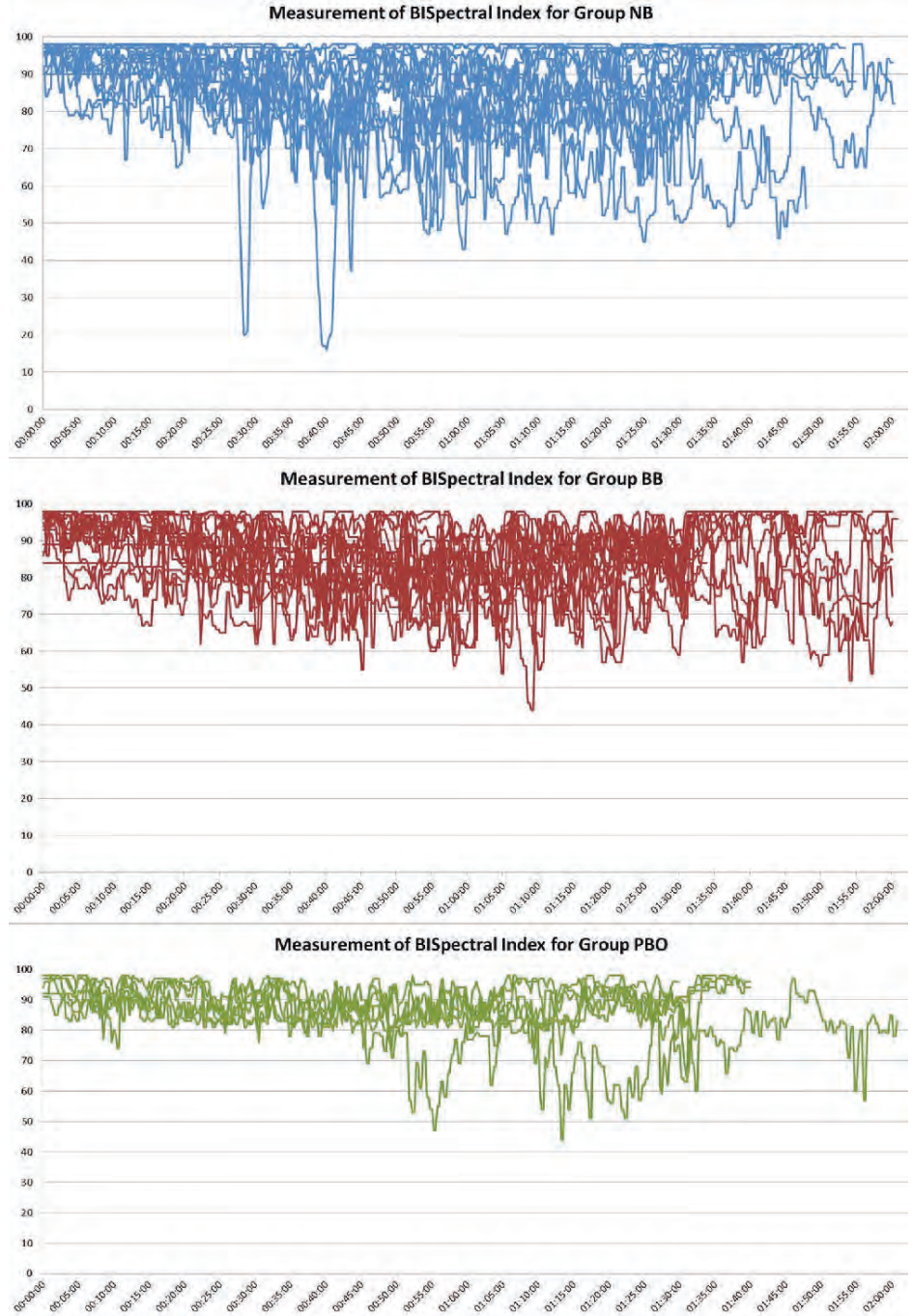

Figure 4-7 Change in BIS