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Original Article

Dose-dependent effects of dexmedetomidine during one-lung ventilation in patients undergoing lobectomy

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Abstract: Determine the dose-dependent effects of dexmedetomidine on anesthetic requirements and cardiopulmonary functions during one-lung ventilation in patients undergoing lobectomy. Sixty patients participated into the study. They wererandomized into four study groups and received placebo (normal saline), low (0.3 μg/kg/hr), intermediate (0.5 μg/kg/hr), or high (0.7 μg/kg/hr) dose of dexmedetomidine. Amount of anesthetic and hemodynamic agents used were documented. Bispectral index, heart rate, mean arterial blood pressure, arterial oxygen partial pressure, and intrapulmonary shunt were recorded at 0 and 10, 20, 30, 40, 50, 60 minutes after dexmedetomidine infusion, and at the end of the operations. No decreased requirements for propofol or sufentanil during anesthesia were observed. High dose of dexmedetomidine (0.7 μg/kg/hr) group required more atropine to maintain hemodynamic stability. Although there were no statistically significant differences in arterial blood gas analyses, patients received intermediate dose of dexmedetomidine (0.5 μg/kg/hr) showed persistent higher values on PaO_2. During one-lung ventilation for lobectomy, dexmedetomidine did not decrease the requirements for propofol and sufentanil administration. Intermediate dose of dexmedetomidine (0.5 μg/kg/hr) might improve oxygenation with no adverse effects on hemodynamic stability. High dose of dexmedetomidine (0.7 μg/kg/hr) required additional hemodynamic stabilizing agent, with no apparent benefit on oxygenation. Future studies with a large sample size are warranted.

Keywords: Dexedetomidine, one-lung ventilation, dose-dependent effects

Introduction

One-lung ventilation (OLV) is used during pulmonary lobectomy to improve exposure to the surgical field [1]. However, OLV can result in significant intrapulmonary shunting and ventilation-perfusion mismatch. Both of them lead to severe hypoxemia [2]. Several approaches have been proposed to overcome hypoxemia during OLV. These include high oxygen insufflation, positive pressure ventilation, and vasoactive agent administration.

Dexmedetomidine is a potent α_2-adrenoceptor agonist with sedative and analgesic activities [4, 5]. It could facilitate anesthesia. It also has both vasoconstriction and vasodilationeffects, and may regulate ventilation-perfusion mismatch and improve oxygenation in patients under OLV. However, only limited studies have been performed to investigate its role during OLV. It was found thatpatients received low dose of dexmedetomidine (0.3 μg/kg/hr) had no obvious improvement in oxygenation [6], while those received high dose of dexmedetomidine (0.7 μg/kg/hr) had better oxygenation, but required additional hemodynamic agents to maintain adequate blood pressure and heart rate [7]. More studies are required to weigh the benefits and adverse hemodynamic effects of dexmedetomidine, thusdetermine whether dexmedetomidine could be recommended for patients to improve their oxygenation with OLV.

The first step in our study was to determine the appropriate dose of dexmedetomidine during OLV. There was no previous study to directly compare different doses of dexmedetomidine in patients under OLV. Here, we report our pilot prospective, randomized, double-blinded, placebo-controlled clinical trial to study the dose-dependent effects of dexmedetomidine in patients receiving OLV. We examined patients' requirements for general anesthetic agents, hemodynamic stability, oxygenation, and pulmonary shunt formation. We hypothesized that

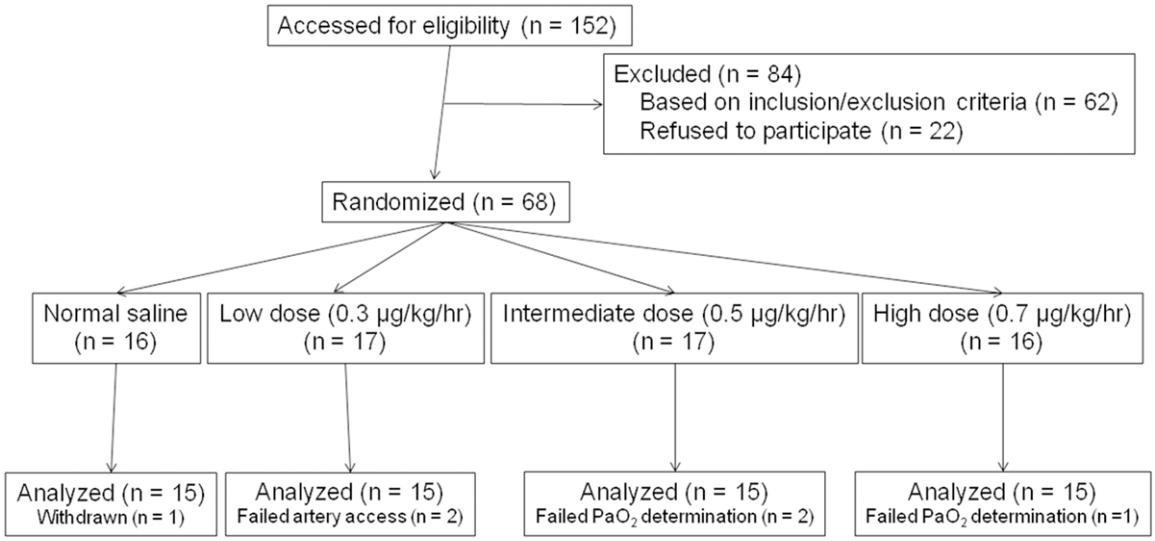

Figure 1. CONSORT flow diagram.

Table 1. Basic characteristics for study participants

	Study groups			
	NS	Dex3	Dex5	Dex7
Age, mean ± SD	55.4 ± 10.7	57.6 ± 8.6	53.8 ± 13.3	62.0 ± 9.2
Gender, male/female	7/8	6/9	7/8	8/7
Weight, kg ± SD	60.5 ± 7.9	59.8 ± 9.4	58.8 ± 10.6	64.1 ± 9.2
Height, cm ± SD	161.9 ± 7.9	164.1 ± 7.7	163.5 ± 8.3	165.9 ± 8.1
Surgical operation, Left/Right lobectomy	6/9	8/7	7/8	7/8
Operational time, min ± SD	121.4 ± 66.4	132.1 ± 55.6	141.0 ± 73.1	109.6 ± 52.4
Preoperative pulmonary function tests				
VT, L ± SD	0.75 ± 0.44	0.71 ± 0.37	0.78 ± 0.32	0.69 ± 0.38
FVC, L ± SD	2.55 ± 0.56	2.61 ± 0.61	2.74 ± 0.33	2.64 ± 0.79
FEV1, L ± SD	2.12 ± 0.59	2.21 ± 0.41	2.15 ± 0.21	2.17 ± 0.69
FEV1/FVC, % ± SD	79.67 ± 6.72	80.13 ± 6.12	78.74 ± 7.52	81.92 ± 5.41
MVV, L ± SD	66.2 ± 10.92	63.7 ± 14.56	57.2 ± 11.97	76.1 ± 27.86

V_T: tidal volume. FVC: forced vital capacity. FEV1: forced expiratory volume in one second. MVV: maximal voluntary ventilation.

an intermediate dose of dexmedetomidine could improve oxygenation without severe adverse effects on the hemodynamic stability. The study results could allow us to calculate the sample size for future studies to define the effects of dexmedetomidine during OLV.

Materials and methods

Study design and participant selection

This was apilot prospective, randomized, double-blinded, placebo-controlled clinical trial performed in an urban academic tertiary care hospital. The study was approved by the Institutional Review Board and registered at Chinese Clinical Trial Registry (ChiCTR, http://www.chictr.org.cn/searchprojen.aspx, # ChiCTRIOR-15006250). The research associates approached the potential candidates during June 1st, 2014 and March 31st, 2015. Inclusion criteria were 18-80 years old, elective pulmonary lobectomy surgery patients, ASA I-II, weight 42-80 kg, and height 150-180 cm. Exclusion criteria were patients with previous allergy history to dexmedetomidine, serious heart or lung disorders, liver or kidney dysfunctions, on antihypertension, anti-arrhythmia, or sedative hypnotic medications, and pregnant women. Basic characteristics (age, gender, weight, height) and pulmonary functions were obtained from every study participant.

Table 2. Amount of anesthetic and hemodynamic agents administrated during OLV

	Study groups			
	NS	Dex3	Dex5	Dex7
Propofol, mg ± SD	527.5 ± 129.0	451.0 ± 108.0	594.8 ± 252.8	565.5±227.1
Sufentanil, μg ± SD	50.5 ± 11.5	54.5 ± 0.5	48.0 ± 10.3	56.6±11.5
Cisatracurium, mg ± SD	8.6 ± 0.6	9.2 ± 0.6	9.7 ± 0.9	8.2±0.6
Ephedrine, mg ± SD	7.4 ± 4.7	7.6 ± 4.9	11.3 ± 5.0	10.5±7.2
Atropine, mg ± SD	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.1	0.2±0.1*

*ANOVA test showed significant differences among four groups. Newman-Keuls test showed that Dex7 required significantly higher amount of atropine when compared to NS, Dex3, and Dex5 individually, $P < 0.05$.

Study protocol

After written informed consents were obtained, the study participants were randomly allocated into four study groups, placebo group (NS, normal saline), low dose (Dex3, 0.3 μg/kg/hr), intermediate dose (Dex5, 0.5 μg/kg/hr), and high dose (Dex7, 0.7 μg/kg/hr) dexmedetomidine group. When the study participants were in the operating room, peripheral access was established and routine continuous monitoring was obtained for vital signs, peripheral capillary oxygen saturation, and five-lead electrocardiography. Arterial blood pressure monitoring and blood gas sampling were performed by inserting a 20G arterial cannula in the right or left radial artery. Central venous pressure was monitored by central venous line placed through the right internal jugular vein into the right atrium and confirmed with X-ray before anesthesia induction. After inducinggeneral anesthesia with midazolam 0.05 mg/kg, sufentanil 0.3-0.4 μg/kg, propofol 1.5-2 mg/kg, andcisatracurium 0.15 mg/kg, bronchial intubation was obtained with Fuji double-lumen tube and confirmed with fiberoptic bronchoscopy. Intermittent positive pressure ventilation was maintained by Primus multiple functional anesthetic machine (FiO_2 100%, I:E 1:2, respiratory rate 12-15 bpm, and $PETCO_2$ 35-45 mmHg). Anesthesia was maintained at bispectral index (BIS) 40-60 by propofol intravenous infusion, sufentanil intermittent administration, and cisatracurium micro-pump injection. Atropine and ephedrine were used when required to maintain hemodynamic stability.

Dexmedetomidine (D-Dexmedetomidine powder, Jiangsu Hengrui Medicine Co., Ltd, catalog # 14031832) 200 μg was diluted in normal saline to 20 ml (10 μg/ml). After induction of anesthesia and obtaining basic blood samples, a bolus dose of dexmedetomidine was given at 1 μg/kg by preparing above solution to 10 ml and infused over 10 min. This was followed by intravenous continuous infusion of dexmedetomidine at 0.3 μg/kg/hr, 0.5 μg/kg/hr, and 0.7 μg/kg/hr for Dex3, Dex5, and Dex7 groups, respectively. Patients in NS group received equivalent volume of normal saline infusion.

Baseline BIS value, heart rate, mean arterial blood pressure, and blood gas samples were obtained after anesthetic induction during two-lung ventilation prior to dexmedetomidine administration. Then, patients were placed in the lateral decubitus position. Dexmedetomidine bolus and infusion were given and OLV was started. BIS value, heart rate, mean arterial blood pressure, and blood gas samples were obtained again at 10 min, 20 min, 30 min, 40 min, 50 min, and 60 min after OLV, and at the time when operations completed.

All the operations were performed by the same team of thoracic surgeon and anesthesia were conducted by the same team of anesthesiologists. Both of them and patients were blinded to the study medication. The study medication-and NS placebo were prepared by one anesthetic nurse and sealed in the envelopes without identification. Patients were not aware the type of medications given to them.

Statistical analysis

Study outcomes included amount of anesthetic and hemodynamic agents administrated, heart rate, mean arterial blood pressure, arterial oxygen partial pressure (PaO_2), intrapulmonary shunt (Qs/Qt), which was calculated by the standard formula [7]. These outcomeswere presented as mean ± standard deviation. The levels of these outcome parameters were compared with ANOVA after checking for normality assumption. If ANOVA test revealed a significant difference, Newman-Keuls test was fur-

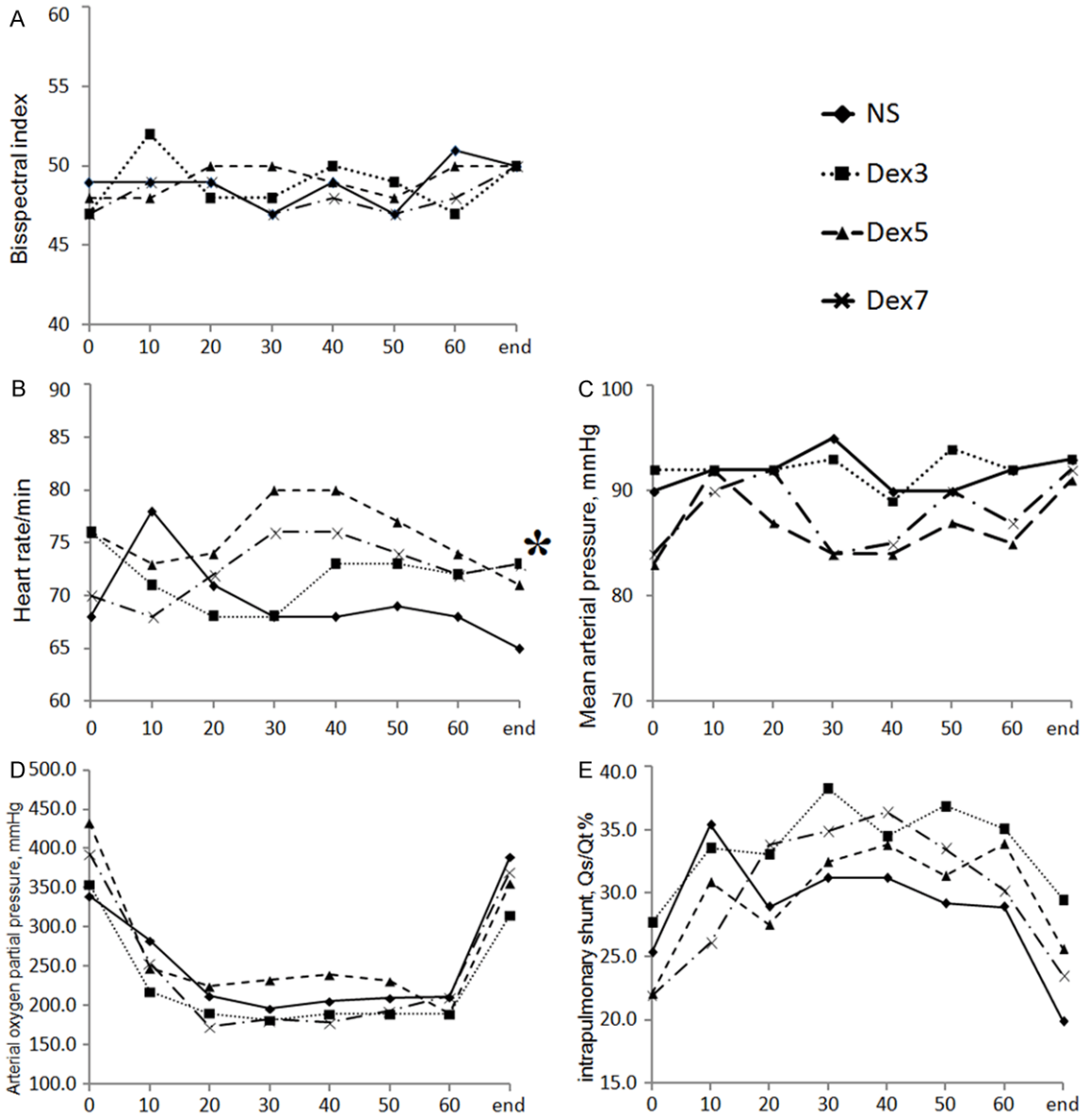

Figure 2. Dose-depended effects of dexmedetomidine during one-lung ventilation. (0 refers to time before dexmedetomidine administration. 10, 20, 30, 40, 50, and 60 refer to 10, 20, 30, 40, 50, and 60 minutes after dexmedetomidine administration. End refers to the time when operations completed). *Patients in Dex7 group required significantly higher dose of atropine to maintain adequate heart rate (see **Table 2**).

ther used to compare the difference between two groups. Statistical analyses were performed with Medcalc software (version 15, Medcalc Software bvba, Ostend, Belgium). A $P < 0.05$ was considered statistically significant.

Results

We screened 152 patients and the final analysis included total 60 patients with 15 patients in each study group. The CONSORT flow diagram is shown in **Figure 1**. The baseline characteristics (age, gender, weight, height, side of surgery, operational time, and pulmonary function tests) were similar among four study groups (**Table 1**).

We did not observe a decreased requirement for propofol, sufentanil, or cisatracurium with different doses of dexmedetomidine administrations (**Table 2**). Doses of administratedephedrine were also similar. However, Dex7 gr-

oup required significantly higher dose of atropine when compared to other study groups (**Table 2**; **Figure 2B**).

The average amount of dexmedetomidine used in each study group was 91.3 ± 40.7, 107.0 ± 46.9, and 120.3 ± 38.0 μg for Dex3, Dex5, and Dex7 group, respectively. Although no statistically significant differences in PaO_2 were observed with increasing doses of dexmedetomidine, patients in the intermediate dose group (0.5 μg/kg/hr) showed persistent better values in PaO_2 at 20-50 min after OLV compared to other groups, (**Figure 2D**; Table S1).

Discussion

In our currentpilot clinical trial, we tested dose-dependent effects of dexmedetomidine during OLV in patients undergoing lobectomy. We did not finddecreased requirements for propofol, sufentanil, or cisatracurium with different doses of dexmedetomidine. Patients in high dose group (0.7 μg/kg/hr) required higher dose atropine to maintain adequate heart rates. Although without statistically significant differences, 0.5 μg/kg/hr dose group showed persistent better oxygenation compared to other groups.

OLV is used during pulmonary lobectomy to facilitate surgery. Due to intrapulmonary shunt formation and ventilation-perfusion mismatch, patients under OLV have high risk to develop severe hypoxemia [3]. Several approaches have been proposed to overcome the hypoxemia during OLV. These include high oxygen insufflation, positive pressure ventilation, and vasoactive agents. Dexmedetomidine has direct vasoconstrictive effects through activation of peripheral α_2-adrenergic receptors [8]. It also has vasodilation effects through activation of central α_2-adrenergic receptors [5]. In addition, dexmedetomidine couldattenuate the local inflammation reactions induced by hypoxic lung ventilation and might have bronchodilatory effects to improve ventilation [9, 10]. Previous studies have suggested that dexmedetomidine could decrease general anesthetic agent requirementsand improve oxygenation [6, 7]. However, in our current dose-dependent clinical trial, we did not observe significant reductions in the requirement for propofol-sufentanil induced anesthesia. At increased dose of dexmedetomidine (0.7 μg/kg/hr), patients required more atropine to maintain adequate hemodynamic stability. This was consistent with previous studies on dexmedetomidine. The only potential benefit effect was observed with intermediate dose (0.5 μg/kg/hr) infusion, patients showed better values in arterial oxygen, without adverse effects on hemodynamic stability.

The limitations of our study included single center, with small sample size and short observation time. The strength of our study was that we studied a relative homogeneous patient population who all received pulmonary lobectomy.

In conclusion, we studied the dose-dependent effects of dexmedetomidine during OLV in patients undergoing lobectomy. We did not found decreased requirements for anesthetic agents. Patients received an intermediate dose of dexmedetomidine (0.5 μg/kg/hr) might have improved oxygenation, without hemodynamic instability. High dose of dexmedetomidine (0.7 μg/kg/hr) required additional hemodynamic agents, without showing beneficiary effects on oxygenation and intrapulmonary shunt formation. Future studies with a large sample size might use 0.5 μg/kg/hras the dose for dexmedetomidine during OLV.

Disclosure of conflict of interest

None.

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Table S1. Dose-dependent effects of dexmedetomidine on sedation and cardiopulmonary functions

	Study groups	BIS value (mean ± SD)	Heart rate (mean ± SD)	Mean arterial blood pressure (MAP, mmHg ± SD)	PaO_2 (mmHg) (mean ± SD)	Qs/Qt (%) (mean ± SD)
T0	NS	49 ± 7	68 ± 9	90 ± 8	339.7 ± 58.5	25.3 ± 7.0
	Dex3	47 ± 7	76 ± 11	92 ± 12	355.1 ± 48.5	27.7 ± 6.3
	Dex5	48 ± 5	76 ± 13	83 ± 11	433.7 ± 58.0	22.1 ± 4.3
	Dex7	47 ± 7	70 ± 11	84 ± 9	393.5 ± 86.3	21.9 ± 8.8
T10	NS	49 ± 6	78 ± 7	92 ± 7	282.8 ± 91.4	35.4 ± 12.0
	Dex3	52 ± 5	71 ± 8	92 ± 6	218.0 ± 104.4	33.6 ± 11.0
	Dex5	48 ± 5	73 ± 11	92 ± 7	247.7 ± 77.1	30.9 ± 4.5
	Dex7	49 ± 5	68 ± 8	90 ± 9	254.2 ± 122.7	26.1 ± 7.7
T20	NS	49 ± 8	71 ± 10	92 ± 7	212.0 ± 99.9	28.9 ± 6.2
	Dex3	48 ± 5	68 ± 9	92 ± 6	190.1 ± 89.5	33.1 ± 10.4
	Dex5	50 ± 7	74 ± 9	87 ± 8	224.7 ± 80.7	27.5 ± 5.8
	Dex7	49 ± 4	72 ± 10	92 ± 9	173.6 ± 90.2	33.8 ± 8.0
T30	NS	47 ± 6	68 ± 9	95 ± 7	196.9 ± 105.0	31.2 ± 9.3
	Dex3	48 ± 5	68 ± 9	93 ± 7	181.5 ± 98.4	38.3 ± 10.0
	Dex5	50 ± 6	80 ± 10	84 ± 11	233.2 ± 107.9	32.5 ± 7.2
	Dex7	47 ± 5	76 ± 9	84 ± 8	182.2 ± 79.1	34.9 ± 8.0
T40	NS	49 ± 6	68 ± 8	90 ± 7	205.5 ± 92.6	31.2 ± 6.5
	Dex3	50 ± 6	73 ± 7	89 ± 5	190.0 ± 104.7	34.5 ± 10.8
	Dex5	49 ± 5	80 ± 11	84 ± 10	239.5 ± 105.7	33.8 ± 4.8
	Dex7	48 ± 6	76 ± 10	85 ± 11	179.2 ± 82.1	36.41 ± 8.0
T50	NS	47 ± 5	69 ± 7	90 ± 7	209.9 ± 80.1	29.2 ± 7.2
	Dex3	49 ± 6	73 ± 9	94 ± 5	189.3 ± 136.7	36.9 ± 11.2
	Dex5	48 ± 5	77 ± 8	87 ± 10	231.8 ± 105.8	31.4 ± 5.3
	Dex7	47 ± 5	74 ± 9	90 ± 12	193.8 ± 93.8	33.5 ± 6.8
T60	NS	51 ± 6	68 ± 8	92 ± 8	211.8 ± 81.0	28.9 ± 8.3
	Dex3	47 ± 6	72 ± 9	92 ± 5	189.3 ± 128.6	35.1 ± 9.3
	Dex5	50 ± 4	74 ± 10	85 ± 10	190.0 ± 79.3	33.9 ± 3.7
	Dex7	48 ± 4	72 ± 10	87 ± 8	212.0 ± 93.0	30.2 ± 4.1
Te	NS	50 ± 5	65 ± 6	93 ± 9	390.4 ± 64.2	19.9 ± 5.3
	Dex3	50 ± 4	73 ± 8	93 ± 6	315.8 ± 81.5	29.5 ± 11.3
	Dex5	50 ± 4	71 ± 8	91 ± 8	356.0 ± 91.3	25.6 ± 9.1
	Dex7	50 ± 6	73 ± 11	92 ± 8	370.7 ± 81.3	23.5 ± 6.0