Assessment of dexmedetomidine effects on left ventricular function using pressure-volume loops in rats

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Assessment of dexmedetomidine effects on left ventricular function using pressure-volume loops in rats

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Kyuho Lee

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ABSTRACT

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The role of dexmedetomidine on left ventricular function is not clearly known. The aim of the present study was to determine whether dexmedetomidine has a myocardial depressive effect by analyzing pressure-volume loops in a rat model.

Thirty-two Sprague-Dawley rats were anesthetized and a pressure-volume loop catheter was advanced via the right carotid artery into the left ventricle. Rats were divided into four groups (n=8 each group). 0.1 ml of normal saline, 1.0, 2.5, and 5.0 μg/kg dexmedetomidine were infused over 10 minutes via the internal jugular vein to the control group, Dex1.0, Dex2.5, and Dex5.0 groups, respectively. Steady-state hemodynamics were recorded. Intermittent inferior vena cava occlusion was done to assess preload-independent indices. Statistical analysis was performed by analysis of variance.

Compared with the control group, changes in Dex1.0 group were insignificant. In Dex2.5 group, only the systolic blood pressure was higher (vs. control, P = 0.03), and other parameters were insignificant. Dex5.0 group

exhibited a lower heart rate, higher systolic blood pressure, higher arterial elastance (vs. control, all $P < 0.001$), and unaltered cardiac output. Dex5.0 group showed steeper slopes of end-systolic pressure increment and end-systolic pressure-volume relationship than the control, Dex1.0, and Dex2.5 groups (all $P < 0.001$). Slopes of end-diastolic pressure decrement and end-diastolic pressure-volume relationship did not differ among groups.

Dexmedetomidine had no direct myocardial depressant effect in the rat heart in doses that are similar to those encountered under clinical conditions. Dexmedetomidine did not significantly alter the ability of the heart to cope with bradycardia and greatly increased afterload. Their potentially negative impact on cardiac output was effectively attenuated by improved myocardial contractility and preserved diastolic function in healthy subjects.

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Key words: dexmedetomidine; pressure-volume loop; left-ventricular function

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I. INTRODUCTION

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is an exceedingly selective α_2-adrenergic agonist with 8-fold higher affinity for the α_2-adrenoceptor than clonidine.[1] It reduces sedative, anxiolytic, and analgesic requirements in the perioperative period without causing significant respiratory depression.[1-3] In addition to its anesthetic-sparing action, potent reduction in sympathetic outflow in response to noxious stimulation made this drug popular as an adjuvant to general anesthesia.[4,5]

Despite these advantages, there are case reports describing adverse events such as intractable cardiac arrest after dexmedetomidine administration.[6-8] The sympatholytic effect, which is accompanied by bradycardia, is thought to account for the decreased cardiac output.[9,10] However, studies found that autonomic denervation did not abolish the cardiovascular effects, implying that the decrease in sympathetic tone was not the sole cause of cardiac dysfunction.[10,11] Although there have been few studies searching for myocardial

depressive effect induced by dexmedetomidine,[11,12] its role on the left ventricular function still remains unclear because alterations in loading conditions interfered precise interpretation of the collected data in previous studies.

Pressure-volume (PV) analysis is a useful approach for examining intact ventricular function independently from loading conditions. Assessing PV loops in human subjects has been restricted due to its invasiveness, but recent validation of miniature PV catheters has made it possible to use this approach for studies in small animals. In the present study we assessed PV loops in a rat model to determine whether dexmedetomidine has depressive effect on left ventricular function.

II. MATERIALS AND METHODS

1. Animal preparation and drug treatment

All procedures of this study were performed in Severance Biomedical Science Institute in Yonsei University College of Medicine, Seoul, South Korea under approval of the Yonsei University Institutional Animal Care and Use Committee. Experiment was performed on 32 male Sprague-Dawley rats that were 3-4 months old and weighed (mean ± SD) 285 ± 14 grams. The rats were allowed to adjust to the controlled laboratory environment for at least 7 days, which consisted of a temperature of 23℃ ± 2℃, humidity of 50% ± 10%, lighting of 350 lux and a light:dark cycle with 12-hour durations. The rats had free access to standard laboratory chow and tap water prior to experiment. Animals were monitored twice daily for health status, and no adverse events were observed during housing period.

Anesthesia techniques that have minimal effects on the animals' heart rates were used.[13] After being anesthetized with an intraperitoneal injection of tiletamine/zolazepam (10 mg/kg; Zoletil, Virbac Laboratories, Carros, France) and 2 % xylazine hydrochloride (2 mg/kg; Rompun, Bayer, Leverkusen, Germany), the rats were placed in the supine position on a temperature-controlled circuit board (Indus Instruments, Houston, TX, USA) with the temperature set to 37 ºC. An inverted T-shaped middle-neck incision from mandible to the sternum was made, and the right carotid artery and the right internal jugular vein were dissected and exposed. A catheter was inserted

in the jugular vein and forwarded into the superior vena cava 0.5 cm above the right atrium for drug administration. A Millar Mikro-Tip conductance catheter (SPR-838, Millar Instruments Inc., Houston, TX, USA) was introduced into the carotid artery and advanced, passing through the aortic valve and into the left ventricle.[14] The signal from the PV catheter was continuously assessed at a sampling rate of 1000 Hz using MPVS-Ultra Single Segment Pressure-Volume Unit (Millar Instruments Inc.). Correct and consistent placement of the PV catheter was based on the PV loop values and overall shape of the generated loops. To perform the inferior vena cava occlusion, a laparotomy was done and a snare was positioned around the inferior vena cava. Then, the rats were allowed to stabilize for 5 minutes before measurement was performed.

After stabilization period, randomization procedure was done by choosing a card from a French playing card deck, which consisted of 4 symbols (spades, hearts, diamonds, and clubs), with 8 cards per symbol. The rats were randomly allocated into four groups according to the selected symbol (n=8 per group). The infusions were prepared by an assistant who mixed the drugs with normal saline to make comparable volume. Therefore, the experimenters were blinded to the pharmacological treatment while processing data. The control group received a 10-minute infusion of 0.1 ml normal saline by the intravenous route. The other three groups (Dex1.0, Dex2.5, and Dex5.0 group) received 1.0, 2.5, and 5.0 μg/kg dexmedetomidine (Hospira, Lake Forest, IL, USA) in the identical fashion, respectively.

2. Assessment of steady-state hemodynamic parameters

The PV loops were assessed for 30 minutes to acquire steady-state hemodynamic variables using PVAN 3.6 software (Millar Instruments Inc.). 10-20 steady-state loops were collected, and the values were averaged from two to three measurements collected over 30 minutes. Also, systolic blood pressure and mean blood pressure were measured by the tail-cuff method. The measured steady-state hemodynamic parameters are as follows: heart rate (HR), systolic blood pressure measured by tail-cuff method (SBP), mean blood pressure measured by tail-cuff method (MBP), left ventricular end-systolic pressure (LVESP), left ventricular end-diastolic pressure (LVEDP), left ventricular end-diastolic volume (LVEDV), stroke volume (SV), stroke work (SW), arterial elastance (E_a), cardiac output (CO), ejection fraction (EF), maximal slope of the end-systolic pressure increment (dp/dt_{max}), maximal slope of the end-diastolic pressure decrement (dP/dt_{min}), and time constant of left ventricular pressure decay (τ).

3. Assessment of preload-independent parameters

To assess left ventricular PV relationships, the inferior vena cava was intermittently occluded by manually pulling the snare for 3 seconds. During inferior vena cava occlusion periods, the slope of the end-systolic pressure-volume relationship (ESPVR), preload recruitable stroke work

(PRSW), and slope of the end-diastolic pressure-volume relationship (EDPVR) using a linear fit were measured.

4. Pressure-volume loop data calibration

Parallel conductance (V_p) was determined individually using a 10-12 μL bolus of 30% saline injected into the right internal jugular vein.[15] The cuvette calibration method (Millar Instruments Inc.) was used to calculate the absolute volume data. Using PVAN 3.6 software, the PV loop data were processed to compute cardiac parameters.[15] At the end of the experiment the animals were sacrificed through heart excision.

5. Statistical analysis

Analyses were performed with GraphPad Prism 5.04 (GraphPad Software, Inc., San Diego, CA, USA). Data are described as means ± SE. Statistical analyses for the comparisons between the groups were performed using one-way analysis of variance by Tukey's multiple comparison test. P values less than 0.05 were considered significant.

III. RESULTS

1. Steady-state hemodynamic parameters

The experiment was successfully completed in all subjects without adverse events. Baseline hemodynamic data are shown in Table 1 and Figure 1. None of the parameters of Dex1.0 group showed significant differences when compared with the control group. In Dex2.5 group, only SBP was higher than that of the control group ($P = 0.03$) and differences in other parameters were insignificant. Dex5.0 group exhibited lower HR, higher SBP, higher E_a (vs. control, all $P < 0.001$), and unaltered CO. MBP, LVESP, and SW of Dex5.0 group were higher than those of the control group and Dex1.0 group (all $P < 0.001$). Particularly, dP/dt_{max} of Dex5.0 group was significantly steeper than that of the other three groups (all $P < 0.001$). Changes in LVEDP, LVEDV, SV, EF, dP/dt_{min}, and Tau of Dex5.0 group were insignificant.

Table 1. Steady-state hemodynamic parameters.

	Control	Dex1.0	Dex2.5	Dex5.0
HR (beats/min)	306.2 ± 7.1	278.0 ± 8.95	272.7 ± 9.1	254.0 ± 6.8*
SBP (mmHg)	100.2 ± 2.7	103.4 ± 3.1	136.1 ± 2.4*	200.2 ± 5.8*†
MBP (mmHg)	80.12 ± 3.2	83.1 ± 4.1	101.7 ± 4.3	161.4 ± 5.8*†
LVESP (mmHg)	99.9 ± 6.5	105.2 ± 5.5	136.8 ± 5.8	201.9 ± 7.5*†
LVEDP (mmHg)	8.8 ± 1.1	10.1 ± 0.8	11.5 ± 1.0	12.5 ± 1.1
LVEDV (μl)	221.4 ± 10.2	235.2 ± 11.5	254.0 ± 13.6	262.9 ± 13.0
SV (μl)	137.4 ± 13.1	151.3 ± 14.2	157.4 ± 12.9	173.0 ± 11.0
SW (mmHg×μl)	10555 ± 897	11692 ± 1263	16348 ± 1362	28912 ± 2027*†
E_a (mmHg/μl)	0.89 ± 0.08	0.88 ± 0.06	1.25 ± 0.08	2.59 ± 0.15*†
CO (μl/min)	42175 ± 1585	41534 ± 1345	40769 ± 1643	44033 ± 1592
EF (%)	62.2 ± 2.3	64.8 ± 3.5	61.3 ± 3.6	66.8 ± 3.5
dP/dt_{max} (mmHg/s)	7720 ± 433	8161 ± 424	8392 ± 509	10901 ± 448*†‡
dP/dt_{min} (mmHg/s)	6331 ± 226	6256 ± 275	6574 ± 310	7884 ± 547
Tau (ms)	12.6 ± 1.3	12.0 ± 1.2	12.4 ± 1.4	14.3 ± 1.6

Values are expressed as mean ± SE. HR, heart rate; SBP, systolic blood pressure measured by tail-cuff method; MBP, mean blood pressure measured by tail-cuff method; LVESP, left ventricular end-systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; SW, stroke work; E_a, arterial elastance; CO, cardiac output; EF, ejection fraction; dP/dt_{max}, maximal slope of the systolic pressure increment; dP/dt_{min}, maximal slope of the diastolic pressure decrement; Tau, time constant of left ventricular pressure decay. Significances indicated by

* P<0.05 vs. the control group, by † P<0.05 vs. Dex1.0 group, by ‡ P<0.05 vs. Dex2.5 group.

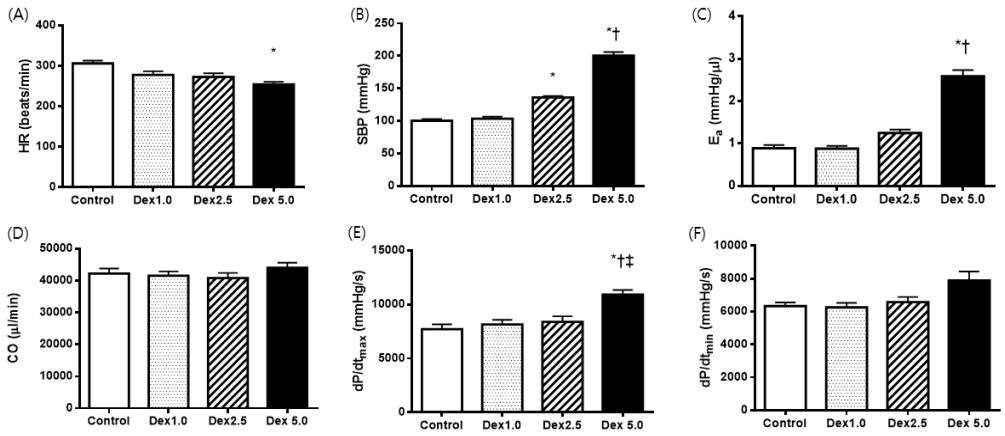

Figure 1. Steady-state hemodynamic parameters. (A) HR, (B) SBP, (C) E_a, (D) CO, (E) dP/dt_{max}, and (F) dP/dt_{min}. Data are mean with error bars showing SE. HR, heart rate; SBP, systolic blood pressure measured by tail-cuff method; E_a, arterial elastance; CO, cardiac output; dP/dt_{max}, maximal slope of the systolic pressure increment; dP/dt_{min}, maximal slope of the diastolic pressure decrement. Significances indicated by * P<0.05 vs. the control group, by † P<0.05 vs. Dex1.0 group, by ‡ P<0.05 vs. Dex2.5 group.

2. Preload-independent parameters

Functional indices derived from PV loop analysis at different preloads are shown in Table 2. Figure 2 depicts representative original PV loops recorded during transient occlusion of the inferior vena cava. Changes in Dex1.0 group and Dex2.5 group were insignificant compared with the control group. The slope of ESPVR in Dex5.0 group was significantly steeper than that of the control group, Dex1.0 group, and Dex2.5 group (all $P < 0.001$). PRSW of Dex5.0 group was also higher than that of the control group and Dex1.0 group (both $P < 0.001$). The slope of EDPVR did not differ between the groups.

Table 2. Preload-independent parameters.

	Control	Dex1.0	Dex2.5	Dex5.0
ESPVR (mmHg/μl)	0.67 ± 0.06	0.69 ± 0.07	0.77 ± 0.06	1.49 ± 0.11*†‡
PRSW (mmHg)	58.6 ± 4.0	59.4 ± 4.8	82.2 ± 5.9	147.2 ± 8.7*†
EDPVR (mmHg/μl)	0.039 ± 0.004	0.036 ± 0.005	0.043 ± 0.007	0.046 ± 0.006

Values are expressed as mean ± SE. ESPVR, end-systolic pressure-volume relationship; PRSW, preload recruitable stroke work; EDPVR, end-diastolic pressure-volume relationship. Significances indicated by * $P<0.05$ vs. the control group, by † $P<0.05$ vs. Dex1.0 group, by ‡ $P<0.05$ vs. Dex2.5 group.

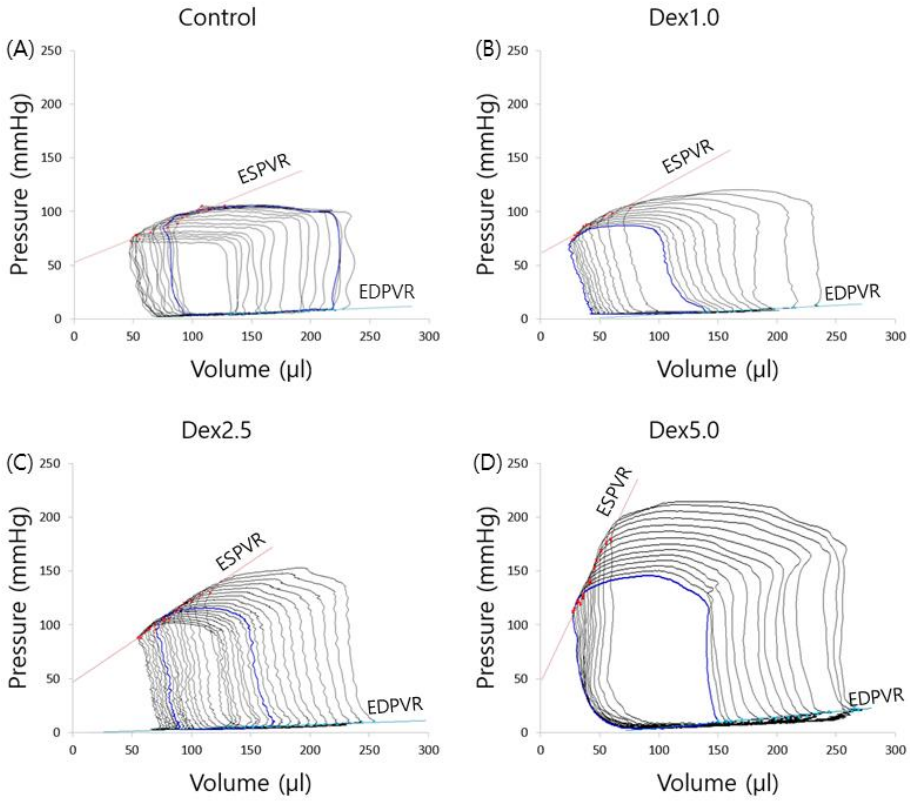

Figure 2. Pressure-volume loops during inferior vena cava occlusion. ESPVR and EDPVR in one representative animal from the control (A), Dex1.0 (B), Dex2.5 (C), Dex5.0 (D) groups are shown. ESPVR, end-systolic pressure-volume relationship; EDPVR, end-diastolic pressure-volume relationship.

IV. DISCUSSION

In the present study we investigated the effect of dexmedetomidine on the left ventricular performance in a rat model. We administered three different doses (1.0, 2.5, and 5.0 μg/kg) and assessed PV loops. The preload-independent parameters were used in order to detect deterioration of left ventricular function. As a result, 1.0 μg/kg and 2.5 μg/kg dexmedetomidine did not induce notable changes. 5.0 μg/kg dexmedetomidine produced prominent bradycardia and hypertension but CO was preserved, which presumably owed to greatly improved myocardial contractility and preserved diastolic function. Our results did not support a direct myocardial depressant action of dexmedetomidine.

The United States Food and Drug Administration recommends a loading infusion of 1.0 μg/kg dexmedetomidine over 10 minutes in clinical practice. However, appropriate dosage guideline for rats is not clearly known, and in previous studies the researchers had administered various doses of dexmedetomidine widely ranging from 1.0 to 100 μg/kg.[16-18] Since extreme doses may exaggerate the drug effect, we sought for doses relevant to human usage. There was an article which the authors consecutively infused 1.0, 2.5, 5.0, 10, and 20 μg/kg and demonstrated that the sedative effect could be observed with lower doses, judged by the loss of righting reflex.[18] Also, a report indicated that the animal dose could be roughly translated to the human equivalent dose by calculating factors based on body surface area of the two species, which are already known.[19] On the basis of these evidences, we selected 1.0, 2.5, and 5.0

μg/kg as our experimental doses, which encompass the normal human dose range.

Our finding suggested that dexmedetomidine infusions of 1.0 and 2.5 μg/kg did not induce significant changes in hemodynamic parameters in rats, whereas the administration of 5.0 μg/kg induced prominent bradycardia. The bradycardia after dexmedetomidine administration is due to the predominant sympatholytic effect, which is characterized by the suppression of plasma catecholamine concentration and cardiac conduction.[20,21] In the past, bradycardia was considered a major cause of the decline in CO after dexmedetomidine administration.[9,10] However, studies found that autonomic denervation did not abolish the peripheral cardiovascular effects, but may even strengthen them, implying that the sympatholytic effect was not the sole cause of cardiac dysfunction.[10,11] Nonetheless, there are differing views on what the other causes of cardiac depression might be. Housman et al.[22] proposed that no negative inotropic effects from dexmedetomidine were observed in isolated canine hearts or in ferret papillary muscles. Flacke et al.[23] hypothesized that α_2-adrenergic agonists could induce coronary vasoconstriction, which could potentially lead to myocardial ischemia. In our study, E_a of Dex5.0 group was markedly higher than that of the control group, suggesting that profound vasoconstriction was induced by 5.0 μg/kg dexmedetomidine. The distinct elevation of LVESP and SBP observed in Dex5.0 group also correlated with this finding, and the

increase in afterload might have played an important role in restricting the cardiac function.

We presumed that dexmedetomidine could directly impair the left ventricular function and thus induce a decline in CO. Interestingly, even in the bradycardic and vasoconstrictive environment, CO was well preserved in Dex5.0 group. Moreover, distinct increase of dP/dt_{max} indicated that myocardial contractility was not suppressed, but enhanced by dexmedetomidine, which could provide an explanation for the preserved CO. Since dP/dt_{max} could be influenced by changes in preload, we applied the inferior vena cava occlusion technique to evaluate preload-independent parameters. The slope of ESPVR, a useful preload-independent measure of contractile function,[24] showed a significant increase in Dex5.0 group. This finding was further supported by an increase in PRSW, which is also a sensitive preload-independent contractility parameter. From these results we could draw the conclusion that dexmedetomidine did not suppress myocardial contractility; instead, a compensatory increase of myocardial contractility was induced to maintain cardiac output in a bradycardic and hypertensive environment. Hence, the depressed ventricular function which occurred after dexmedetomidine administration in previous reports[11,12] could have been due to factors other than direct depression of the myocardium.

The increase of ventricular contractility is seldom observed in previous studies associated with dexmedetomidine. Although our findings clearly indicate that

dexmedetomidine did not suppress myocardial contractility, there is a possibility that increased ventricular contractility was a result of complex cardiovascular homeostatic mechanism, rather than an effect induced by dexmedetomidine. Unfortunately, we could not verify such hypothesis in the present study. According to our knowledge, only one article reported inotropic effect induced by dexmedetomidine.[10] The authors reported that extreme doses which are far beyond doses maximally effective in intact animals could release catecholamines from cardiac stores, accompanied by positive inotropic and positive chronotropic effects. However, doses involved in the present study were much lower, and we could not observe any increase in HR. Therefore, it seems premature to conclude that dexmedetomidine increased myocardial contractility.

An article reported that dexmedetomidine increased LVEDP, suggesting impaired diastolic function.[23] However, our results demonstrated that LVEDP remained stable regardless of the administrated doses. The slope of EDPVR did not differ between the groups, which indicated unchanged LV stiffness in all groups. In addition, other diastolic parameters such as Tau and dP/dt_{min} behaved in an identical fashion, which strengthened our view that dexmedetomidine had no distinct effect on diastolic function. However, there is an evidence that dexmedetomidine impaired diastolic function in subjects with pre-existing heart disease,[25] and it must be pointed out that our study included only young and healthy rats. It is questionable whether the diastolic function could still be

preserved if our experiment were conducted on incompetent hearts, and this issue deserves further investigation.

Dexmedetomidine has complex direct vascular effects, because it can induce both vasoconstriction and vasodilation, due to the presence of two different subtypes of α_2-adrenoceptor: the α_{2A}-adrenoceptor is responsible for vasodilation, whereas the α_{2B}-adrenoceptor induces vasoconstriction.[26] Specifically, vasoconstriction is due to contraction of vascular smooth muscle regulated by Ca^{2+}-dependent or Ca^{2+}-sensitization mechanism,[27,28] and vasodilation is associated with the action of endothelial nitric oxide synthase within the vascular endothelium.[29] However, how these two opposing tendencies interact with each other is not clear. In an attempt to explain the biphasic response, one article suggested that an initially predominant vasoconstriction effect was abolished by a vasodilation effect as time elapsed.[30] Nonetheless, the time course of changes in blood pressure after dexmedetomidine administration is still not well established. Although there is evidence suggesting that the initial hypertension lasted for 5 to 10 minutes,[31] the time required to observe the biphasic response varied among studies.[23,32] Since the optimal time was not clear, we arbitrarily set the time of measurement at 30 minutes.

Limitations of this study are as follows; although our measurement time was adequate to assess steady-state PV loop variables, we could not observe the biphasic change in blood pressure. However, we could not extend our

observation time because prolonged maintenance of the PV catheter might by itself have negatively affected the hemodynamic stability. Also, interspecies difference cannot be excluded.

V. CONCLUSION

The clinically relevant finding of this study is that dexmedetomidine had no direct myocardial depressant effect in the rat heart in doses that are similar to those encountered under clinical conditions. Dexmedetomidine did not significantly alter the ability of the heart to cope with bradycardia and greatly increased afterload. Their potentially negative impact on CO was effectively attenuated by improved myocardial contractility and preserved diastolic function in healthy subjects.

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ABSTRACT(IN KOREAN)

백서에서 덱스메데토미딘이 좌심실 기능에 미치는 영향의 압력-용적 고리를 통한 분석

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덱스메데토미딘이 좌심실 기능에 어떠한 영향을 미치는가에 대해서는 아직 명확하게 밝혀진 바가 없다. 본 연구에서는 백서 모델에서 압력-용적 고리의 분석을 통해 덱스메데토미딘이 좌심실 기능의 저하를 일으키는지 알아보고자 하였다.

서른 두 마리의 백서를 마취시킨 후 압력 용적 고리 카테터를 우측 경동맥으로 삽입하여 좌심실까지 진입시켰다. 백서는 각 군당 8마리의 네 군 (대조군, Dex1.0군, Dex2.5군, Dex5.0군)으로 나누어서 각각 생리식염수 0.1밀리리터, 덱스메데토미딘 1.0, 2.5, 5.0 μg/kg을 10분에 걸쳐 오른쪽 내경정맥을 통해 주입하였다. 약물 주입 후 안정된 상태에서 혈역학적 데이터를 기록하였다. 그 후 하대정맥을 간헐적으로 폐쇄시키면서 전부하에 독립적인 지표들을 기록하였다. 통계분석은 일원배치 분산분석 방식으로 시행하였다.

Dex1.0군은 대조군과 비교하였을 때 유의미한 차이가 없었다. Dex2.5군에서는 수축기 혈압만이 대조군에 비해 높은 것으로 관찰되었다 (P = 0.31). Dex5.0군에서는 유의미하게 낮은 심박동수, 높은 수축기 혈압, 높은 동맥탄성도가 관찰되었으나 (P < 0.001), 두 군간 심박출량의 차이는 관찰되지 않았다. 또한, Dex5.0군에서는 수축기말 압력증가의 기울기와 수축기말 압력-용적 관계가 다른 세 군에 비해 유의미하게 높았다 (P < 0.001). 하지만 이완기말 압력감소의 기울기나 이완기말 압력-용적 관계는 모든 군에 있어 유의미한 차이는 관찰되지 않았다.

임상에서 활용되는 용량의 덱스메데토미딘을 쥐에게 투여한 결과 직접적인 심근저하 효과는 관찰되지 않았다. 덱스메데토미딘 투여로 인해 유의미한 수준의 서맥과 후부하 증가가 발생하였지만, 심근 수축력 또한 향상되어 심박출량의 저하를 억제하고 정상적인 수준으로 유지시키는 데 기여한 것으로 판단된다.

핵심되는 말 : 덱스메데토미딘; 압력-용적 고리; 좌심실 기능