Title	Felypressin, but not epinephrine, reduces myocardial oxygen tension after an injection of dental local anesthetic solution at routine doses
Author(s) Alternative	Inagawa, M; Ichinohe, T; Kaneko, Y
Journal	Journal of oral and maxillofacial surgery, 68(5): 1013-1017
URL	http://hdl.handle.net/10130/1589
Right	

Elsevier Editorial System(tm) for Journal of Oral and Maxillofacial Surgery
Manuscript Draft

Manuscript Number: JOMS-D-09-00100R1

Title: Felypressin, But Not Epinephrine, Reduces Myocardial Oxygen Tension after an Injection of Dental Local Anesthetic Solution at a Routine Doses

Article Type: Unspecified Article Type

Keywords: local anesthetics; Felypressin; Epinephrine; Myocardial oxygen balance

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Abstract: Purpose: The aim of this study was to evaluate the effect of epinephrine (Epi) or felypressin (Fely) contained in dental local anesthetics on myocardial oxygen balance.
Methods: Male Japan White tracheotomized rabbits were anesthetized with isoflurane. Three doses of 0.18, 0.36, and 0.72 ml of 2% lidocaine hydrochloride containing 1: 80,000 Epi or 3% prilocaine hydrochloride containing 0.03 IU/ml Fely were injected into the rabbit tongue muscle. These doses were equivalent to 2, 4, and 8 of dental local anesthetic cartridges in humans weighing 50 kg by body weight correction, respectively. Heart rate (HR), blood pressure, aortic blood flow (AoF), myocardial tissue blood flow (MBF) and myocardial tissue oxygen tension (PmO2) were continuously monitored. Data were recorded immediately before and 10, 20, 30 and 60 min after the injection.
Results: HR decreased in Fely group. Systolic blood pressure elevated in Epi group, while diastolic blood pressure elevated in both groups. AoF and MBF increased while PmO2 did not change in Epi group. In contrast, AoF, MBF and PmO2 decreased in Fely group.

Conclusion: It is suggested that Fely, but not Epi, would reduce myocardial oxygen tension and aggravate myocardial oxygen demand/supply balance even after an injection of dental local anesthetic solution at routine doses.

* Revision Cover Letter (with Revision Notes)

29th April, 2009

Dr. Leon A. Assael
Editor-in-Chief
Journal of Oral and Maxillofacial Surgery

RE **JOMS-D-09-00100**: "**Felypressin, But Not Epinephrine, Reduces Myocardial Oxygen Tension after an Injection of Dental Local Anesthetic Solution at a Routine Doses**"

Dear Sir,

Attached, please find our manuscript entitled "Felypressin, But Not Epinephrine, Reduces Myocardial Oxygen Tension after an Injection of Dental Local Anesthetic Solution at a Routine Doses" which we are resubmitting for consideration to Journal of Oral and Maxillofacial Surgery, as an amended version.

According to the reviewers' thoughtful and suggestive comments, we revised the manuscript. The revised parts are listed in the following paper.

We hope you will appreciate the significance of our intention, and look forward to your favorable decision.

Sincerely yours,

Motoaki Inagawa, DDS, PhD

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29th April, 2009

Dear the editor-in-chief and reviewers

Thank you very much for kindly reviewing our manuscript and giving us valuable comments and suggestions. We have made revisions based on these comments and suggestions. Please find point-to-point descriptions of how we responded to the reviewer's comments, suggestions, and criticisms. We hope the revision meets the demand by the editor and reviewers, and that our revised manuscript will be acceptable for publication in the Journal of Oral and Maxillofacial Surgery.

Reviewer #1

Comment 1:

Since felypressin is not available in the US I would provide more background information about its use in local anesthesia and what is believed to be its advantages and disadvantages.

Response:

We revised the manuscript and add following sentences,

INTRODUCTION: Page 3, Lines 5-9

"Fely (2-phe-8-lys vasopressin) is a synthetic hormone that has similar structure with vasopressin.[1, 7] Because Fely is not classified as a catecholamine, it had been believed to have fewer influences on the cardiovascular system than Epi.[1, 2, 7-9] Therefore, Fely has been applied to the patients compromised with circulatory diseases as a safe vasoconstrictor in Japan and European Union nations.[2, 7, 9]"

Comment 2

There is some editing that has to be done pertaining to language but I would otherwise accept the manuscript. I feel that this manuscript is with minor modifications to be accepted.

Response:

We totally revised our manuscript as clearly as we can.

Felypressin, But Not Epinephrine, Reduces Myocardial Oxygen Tension after an Injection of Dental Local Anesthetic Solution at a Routine Doses

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ABSTRACT

Purpose: The aim of this study was to evaluate the effect of epinephrine (Epi) or felypressin (Fely) contained in dental local anesthetics on myocardial oxygen balance.

Methods: Male Japan White tracheotomized rabbits were anesthetized with isoflurane. Three doses of 0.18, 0.36, and 0.72 ml of 2% lidocaine hydrochloride containing 1: 80,000 Epi or 3% prilocaine hydrochloride containing 0.03 IU/ml Fely were injected into the rabbit tongue muscle. These doses were equivalent to 2, 4, and 8 of dental local anesthetic cartridges in humans weighing 50 kg by body weight correction, respectively. Heart rate (HR), blood pressure, aortic blood flow (AoF), myocardial tissue blood flow (MBF) and myocardial tissue oxygen tension (PmO_2) were continuously monitored. Data were recorded immediately before and 10, 20, 30 and 60 min after the injection.

Results: HR decreased in Fely group. Systolic blood pressure elevated in Epi group, while diastolic blood pressure elevated in both groups. AoF and MBF increased while PmO_2 did not change in Epi group. In contrast, AoF, MBF and PmO_2 decreased in Fely group.

Conclusion: It is suggested that Fely, but not Epi, would reduce myocardial oxygen tension and aggravate myocardial oxygen demand/supply balance even after an injection of dental local anesthetic solution at routine doses.

INTRODUCTION

Vasoconstrictors such as epinephrine (Epi) and felypressin (Fely) are contained in dental local anesthetics to enhance anesthetic effects and to reduce bleeding of the surgical field.[1] There have been many reports that alert the use of dental local anesthetics containing Epi to patients with cardiovascular diseases.[1-6] Fely (2-phe-8-lys vasopressin) is a synthetic hormone that has similar structure with vasopressin.[1, 7] Because Fely is not classified as a catecholamine, it had been believed to have fewer influences on the cardiovascular system than Epi.[1, 2, 7-9] Therefore, Fely has been applied to the patients compromised with circulatory diseases as a safe vasoconstrictor in Japan and European Union nations.[2, 7, 9] However, there are some reports that the clinical dose of Fely or vasopressin induced myocardial ischemia during surgery.[10, 11] Therefore, we consider that it is important to elucidate whether Fely is safer than Epi when used in patients with cardiovascular diseases.

A small dose infusion of Fely has inhibitory effects on cardiac function and causes a decrease in coronary blood flow, whereas these changes did not affect myocardial oxygen balance evaluated with calculated variables in a dog experiment.[12] This result suggests that a small dose of Fely does not aggravate myocardial oxygen balance. However, this study did not monitor myocardial tissue oxygen tension (PmO_2), which is a direct indicator of myocardial oxygen balance.

Agata reported that a small dose infusion of Fely decreased coronary blood flow and left ventricular inner layer PmO_2 in a dog experiment.[13] This result clearly suggests possible myocardial ischemia after the use of Fely. However, in this study, Fely was administered intravenously without a concomitant use of a local anesthetic. Therefore, it may be difficult to extrapolate these results to routine dental practices. Miyachi injected 3% prilocaine

hydrochloride solution containing 0.03 IU/ml Fely for dental use into the tongue muscle in the dog and investigated the myocardial oxygen balance by monitoring PmO_2.[14] As a result, it is suggested that an injection more than 3 - 6 cartridges of the solution may reduce myocardial oxygen tension. However, there is no report that compared myocardial oxygen tension after the use of clinically relevant doses of Epi and Fely under the same experimental condition with direct monitoring of PmO_2.

In this study, we compared the effects of Epi or Fely contained in local anesthetic solutions injected into the rabbit tongue muscle on the myocardial oxygen balance by monitoring myocardial tissue blood flow (MBF) and PmO_2.

MATERIAL AND METHODS

All animals received humane care in accordance with the Guideline for the Treatment of Experimental Animals approved by Tokyo Dental College, Chiba, Japan. Male Japan White rabbits weighing 2.3 - 2.7 kg were purchased from SLC (Tokyo, Japan). Six rabbits received an intramuscular injection of 2 % lidocaine hydrochloride solution containing 1:80,000 Epi (Xylesthesin A, 3M Health Care, Tokyo) at a dose of 0.18 ml (E2 group), 0.36 ml (E4 group) and 0.72 ml (E8 group) into the tongue muscle. The other 6 rabbits received 3 % prilocaine hydrochloride solution containing 0.03 IU/ml Fely (Citanest-Octapressin, Dentsply-Sankin, Tokyo) at a dose of 0.18 ml (F2 group), 0.36 ml (F4 group) and 0.72 ml (F8 group). Animals were housed in an air-conditioned room (24.0 ± 3.0 °C and 65 ± 5 % humidity) regulated by light and dark cycle every 12 hour and given commercial laboratory chow and water *ad libitum* until the experiment.

Anesthesia was induced and maintained with oxygen and isoflurane. Before skin incisions for each of the experimental procedures, appropriate doses of lidocaine hydrochloride were injected into the surgical field. A #20 French non-cuffed endotracheal tube was inserted into the trachea via a tracheotomy. A 22 gauge Teflon catheter was inserted into the left marginal auricular vein for infusion. A 20 gauge Teflon catheter was inserted into the right femoral artery. Femoral artery blood pressure was continuously monitored with a pressure transducer (P231D; Gould, Oxnard, California). Heart rate (HR) was recorded by a tachograph triggered by the blood pressure wave. After muscle relaxation was obtained with an intravenous administration of alcuronium chloride, rabbits were mechanically ventilated. A left thoracotomy was performed at the 5th intercostal space. A flow probe (Type 3B, Transonic Systems, Ithaca, New York) was fixed and aortic blood flow (AoF) was continuously monitored using an ultrasonic blood

flowmeter (T108, Transonic Systems, Ithaca, New York). A needle electrode (UHE - 100, Unique Medical, Tokyo) was inserted and fixed at 3 mm depth in the myocardial tissue supplied by the left anterior descending artery. MBF was monitored using a hydrogen clearance tissue blood flowmeter (MGH - D1, Unique Medical, Tokyo). A polarographic needle electrode (POE - 40 PDS, Inter Medical, Tokyo) was inserted and fixed at the same region of the myocardium with 3 mm distance from the needle electrode for MBF monitoring. PmO_2 was continuously monitored using a tissue PO_2 meter (PO_2 - 100DW, Inter Medical, Tokyo). Acetated Ringer's solution was infused at 10 ml/kg/hr. Body temperature was kept 39.0 – 39.5 °C using a heat lamp. All data except MBF were continuously recorded on a polygraph (Series360 NEC; Sanei, Tokyo).

After the finish of experimental preparations, 60 minutes was elapsed for hemodynamic stabilization. After the control values were recorded, 0.18 ml of the local anesthetic solution containing Epi or Fely was injected. Data were recorded 10, 20, 30 and 60 minutes after the injection. Following the final recording at 60 minutes after the injection, 30 - 60 minutes was elapsed for the recovery of hemodynamic variables. Then, next series (0.36 ml and then 0.72 ml) of the observations were repeated.

One-way ANOVA for repeated measurements were used for intragroup comparisons. Student-Newman-Keuls test was used for multiple comparisons. Student t-test was used for intergroup comparisons. A *P* value less than 0.05 was considered to be statistically significant.

RESULTS

HR decreased in F2, F4 and F8 groups. Systolic blood pressure (SBP) elevated in E4 and E8 groups in a dose-dependent manner. Diastolic blood pressure (DBP) elevated in E4, E8, F4 and F8 groups. Mean arterial pressure (MAP) elevated in E4 and E8 groups. AoF increased in E4 and E8 groups in a dose-dependent manner. In contrast, AoF decreased in F2, F4 and F8 groups in a dose-dependent manner (Table 1).

MBF increased in E2, E4 and E8 groups in a dose-dependent manner. In contrast, MBF decreased in F2, F4 and F8 groups in a dose-dependent manner (Fig. 1). PmO_2 decreased in F2, F4, and F8 groups in a dose-dependent manner (Fig. 2). Reductions in MBF and PmO_2 in Fely group reached their maximums 20 - 30 min after Fely injection.

DISCUSSION

In the present study, 0.18, 0.36 and 0.72ml of the local anesthetic solutions were injected to the rabbit's tongue muscle. These doses were equivalent to 2, 4 and 8 cartridges of a dental local anesthetic solution in humans weighing 50 kg by body weight correction. Two cartridges of a dental local anesthetic solution were frequently used in routine dental practices. In addition, 4 - 8 cartridges were possibly used in oral surgery such as in dental implant or periodontal surgeries. Therefore, present experimental situations may be relevant for clinical dental practices.

SBP, DBP, MAP and AoF increased in a dose-dependent manner after Epi administration. These changes were attributable to positive inotropic effects of Epi.[15, 16] Tachycardia induced by isoflurane[17] might in part blunt HR increase after Epi administration. After Fely administration, SBP and MAP did not change, whereas DBP increased. HR and AoF decreased in a dose-dependent manner. These changes were attributable to the inhibitory effect of Fely on cardiac functions[12, 18] and peripheral vasoconstriction[14, 19, 20] induced by Fely. In addition, vasoconstricting effects of prilocaine[21] might in part contribute to the increase in DBP.

MBF increased after Epi administration, whereas it decreased after Fely administration. At the same time, PmO_2 did not change after Epi administration, whereas it decreased after Fely administration. Although myocardial oxygen consumption increases through cardiac acceleration by Epi[15], it may be compensated by an increase in myocardial oxygen supply based on the MBF increase. No change in PmO_2 suggests that myocardial oxygen balance was preserved after Epi administration in the present study. In contrast, cardiac work was apparently reduced by decreases in HR and AoF after Fely administration. If MBF decrease was relative to the reduction in cardiac work, PmO_2 would be maintained throughout the study. However, PmO_2 showed a dose-dependent decrease, which suggested deterioration of myocardial oxygen balance.

It is therefore suggested that the decrease in myocardial oxygen supply based on MBF decrease through the coronary vasoconstriction by Fely[12-14] exceeded the decrease in myocardial oxygen demand based on cardiac depression by Fely.[12]

Ten percent decrease of the control value in PmO_2 produces functional disturbance of the heart[22], and 40% decrease in PmO_2 increases the risk of ventricular fibrillation.[23] In the present study, the maximum decreases in PmO_2 were about 6, 11 and 24 % in F2, F4 and F8 groups, respectively. Therefore, it is suggested that the use of 4 - 8 cartridges of a dental local anesthetic solution containing Fely may reduce myocardial oxygen tension and increase the risk of ventricular arrhythmias. These results agree with previous studies reporting that the use of more than 3 - 6 cartridges in humans may reduce myocardial oxygen tension.[14, 18]

In the present study, PmO_2 was maintained after Epi administration. However, increases in SBP and AoF are necessarily followed by the increase in myocardial oxygen consumption and may reduce myocardial oxygen tension in the patients with cardiovascular diseases.

Rabbit was used to evaluate myocardial oxygen balance as an experimental animal in the present study. Rabbit have few collateral coronary arteries, which are similar to those in humans.[24] In the present study, PmO_2 is continuously monitored at 3 mm depth in the myocardial tissue. Although the deeper sub-endocardial region might be more prone to myocardial ischemia[25], it was difficult to fix the needle electrode at this region because the thickness of the left ventricular myocardium was 4 - 5 mm. Potential risk of electrode penetration into the left ventricle must be avoided.

In the present study, control value in PmO_2 at F8 was larger than those at F2 and F4. However, the difference was only 3 mmHg, and should minimally affect the results. Control value in MBF in F4 was larger than that at F8. However, PmO_2 at F8 was well preserved and

slightly higher than that at F4. Therefore, it is suggested that myocardial damage after prolonged Fely infusion might be minimal.

In conclusion, Fely decreased PmO_2 and aggravated myocardial oxygen demand /supply balance after a routine dose injection of dental local anesthetic solution. Fely cannot be applied more safely to the patients with cardiovascular diseases than Epi.

ACKNOWLEDGMENTS

This study was partially supported by Grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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FIGURES LEGEND

Fig. 1 Percent changes in myocardial tissue blood flow (MBF) after injection of 2 % lidocaine hydrochloride solution containing 1:80,000 Epi or 3 % prilocaine hydrochloride solution containing 0.03 IU/ml Fely at a dose of 0.18 ml (E2, F2 group), 0.36 ml (E4, F4 group) and 0.72 ml (E8, F8 group). Data are shown as mean ± standard deviation.

* $P < 0.05$ vs. control

Fig. 2 Percent changes in myocardial tissue oxygen tension (PmO_2) after injection of 2 % lidocaine hydrochloride solution containing 1:80,000 Epi or 3 % prilocaine hydrochloride solution containing 0.03 IU/ml Fely at a dose of 0.18 ml (E2, F2 group), 0.36 ml (E4, F4 group) and 0.72 ml (E8, F8 group). Data are shown as mean ± standard deviation.

* $P < 0.05$ vs. control

Figure

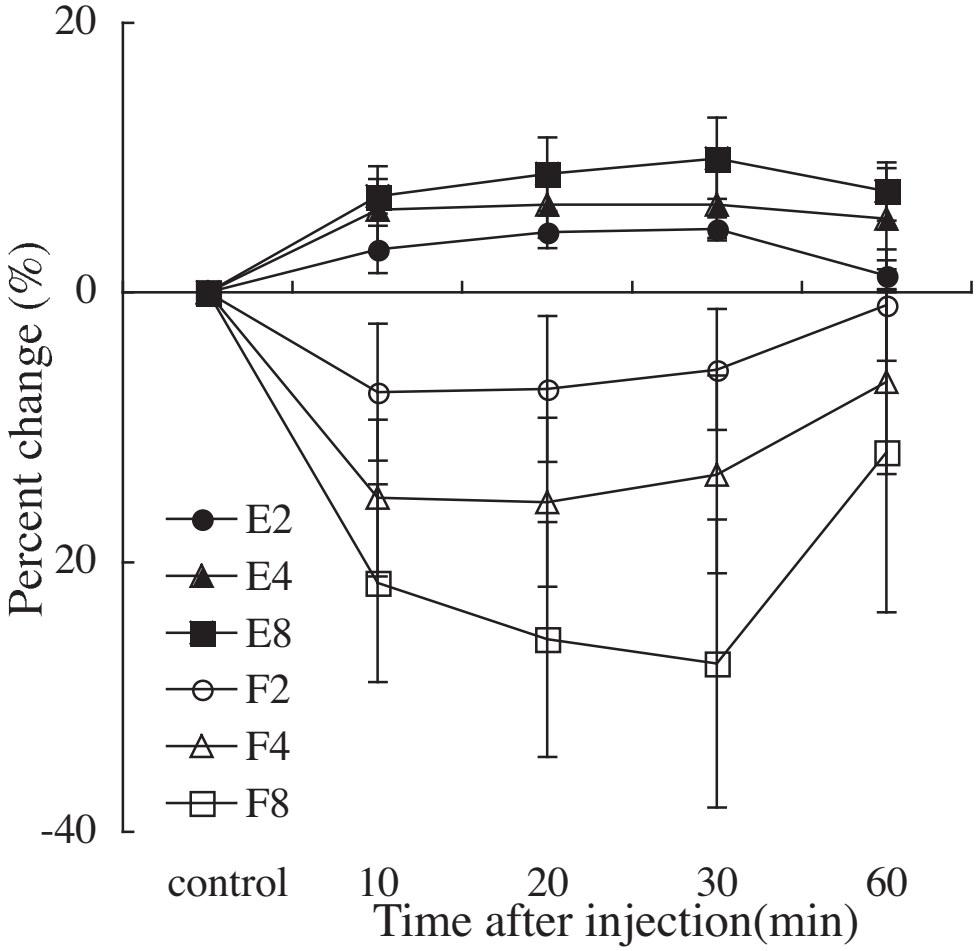
20
0
20
-40
Percent change (%)
E2
E4
E8
F2
F4
F8
control
10
20
30
60
Time after injection(min)

Fig. 1

Figure

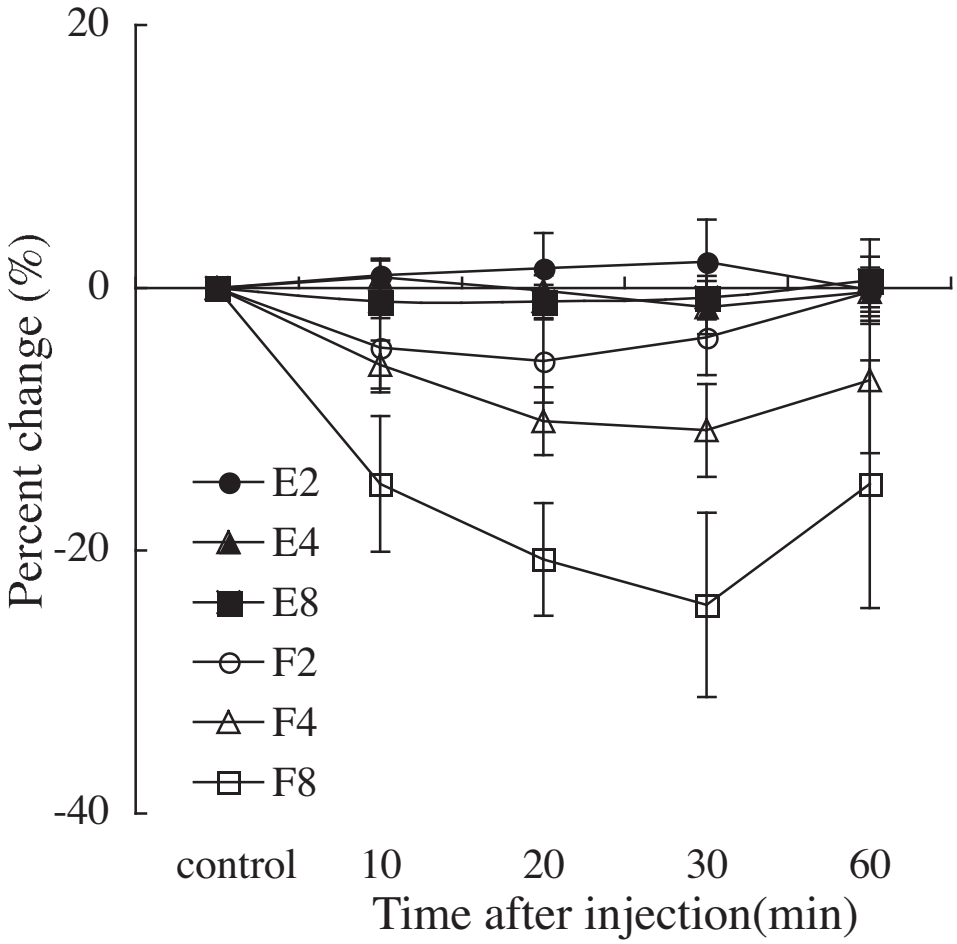
20
0
-20
-40
Percent change (%)
E2
E4
E8
F2
F4
F8
control
10
20
30
60
Time after injection(min)

Fig. 2

Table

Table 1 Hemodynamic changes after the injection of 2 % lidocaine hydrochloride solution containing 1: 80,000 Epi or 3 % prilocaine hydrochloride solution containi
group), 0.36 ml (E4, F4 group) and 0.72 ml (E8, F8 group).

E2		control	Time (min)			
			10	20	30	60
HR(bpm)	mean	248.3	248.8	249.5	250.3	247.7
	SD	33.3	35.8	34.5	32.1	31.2
SBP(mmHg)	mean	109.5	117.0	116.7	114.0	111.8
	SD	4.6	7.2	7.5	5.5	6.2
DBP(mmHg)	mean	65.8	68.4	67.2	67.0	65.6
	SD	10.8	8.5	7.1	8.0	8.9
MBP(mmHg)	mean	80.3	84.8	84.0	82.5	81.0
	SD	8.3	7.5	6.4	6.5	6.9
AoF(ml/min)	mean	344.3	354.7	350.7	351.3	350.7
	SD	30.0	33.7	32.6	32.9	35.0
MBF(ml/min/100g)	mean	71.5	73.6*	74.6*	74.8*	72.5
	SD	1.3	1.4	1.5	0.9	1.0
PmO_2(mmHg)	mean	69.6	70.4	71.0	71.0	69.2
	SD	5.8	6.1	5.1	5.2	5.3

E4		control	Time (min)			
			10	20	30	60
HR(bpm)	mean	240.0	241.8	236.7	239.8	244.5
	SD	25.2	25.2	25.1	25.1	24.1
SBP(mmHg)	mean	109.0	118.5*	117.8*	113.6	110.2
	SD	7.2	7.8	11.1	8.1	8.4
DBP(mmHg)	mean	63.6	69.8*	68.3*	66	65.2
	SD	4.7	3.0	3.1	2.0	2.8
MBP(mmHg)	mean	78.7	85.5*	84.8*	81.9	80.2
	SD	4.2	2.5	4.9	3.5	3.1
AoF(ml/min)	mean	344.2	365.5*	360.5*	355.5*	357.0*
	SD	30.6	26.9	31.4	34.3	30.7
MBF(ml/min/100g)	mean	70.5	74.8*	75.0*	75.0*	74.4*
	SD	3.7	2.8	3.0	3.2	3.1
PmO_2(mmHg)	mean	66.0	66.6	65.8	64.8	65.6
	SD	4.6	3.8	4.2	4.4	5.2

E8	
HR(bpm)	mean
	SD
SBP(mmHg)	mean
	SD
DBP(mmHg)	mean
	SD
MBP(mmHg)	mean
	SD
AoF(ml/min)	mean
	SD
MBF(ml/min/100g)	mean
	SD
PmO_2(mmHg)	mean
	SD

F2		control	Time (min)			
			10	20	30	60
HR(bpm)	mean	279.0	272.2	268.4*	270.2*	274.0
	SD	23.5	32.0	33.1	32.8	25.9
SBP(mmHg)	mean	120.2	115.5	112.5	114.8	115.5
	SD	5.3	8.2	11.6	10.7	8.9
DBP(mmHg)	mean	72.8	72.6	72.8	73.2	72.8
	SD	8.8	7.5	6.7	7.7	9.0
MBP(mmHg)	mean	87.7	86.9	85.9	87.1	86.9
	SD	4.5	4.3	4.5	4.8	5.4
AoF(ml/min)	mean	346.8	338.8*	333.4*	338.6*	342.6*
	SD	44.9	47.0	49.7	50.3	53.8
MBF(ml/min/100g)	mean	73.5	68.2*	68.2*	69.4*	72.6
	SD	4.0	7.7	7.3	6.7	6.2
PmO_2(mmHg)	mean	67.2	64.5*	63.0*	64.5*	67.0
	SD	5.0	6.1	6.1	5.7	5.8

F4		control	Time (min)			
			10	20	30	60
HR(bpm)	mean	266.2	249.4*	238.2*	273.8*	238.0*
	SD	19.2	20.5	13.0	12.7	17.1
SBP(mmHg)	mean	111.3	110.6	113.0	111.2	111.6
	SD	6.6	6.2	7.8	7.6	7.6
DBP(mmHg)	mean	72.8	76.0	78.0*	76.2	78.8*
	SD	9.9	7.3	6.9	6.9	6.3
MBP(mmHg)	mean	85.1	87.5	89.5	87.9	89.5
	SD	7.2	6.5	6.3	6.0	5.3
AoF(ml/min)	mean	341	320.0*	317.8*	321.2*	329.6*
	SD	39.4	33.5	44.0	48.0	45.5
MBF(ml/min/100g)	mean	75.4	63.1*	62.9*	64.7*	69.6*
	SD	4.4	3.8	4.1	5.2	4.3
PmO_2(mmHg)	mean	66.0	62.3*	59.3*	59.3*	61.5*
	SD	4.4	5.4	5.7	1.4	1.5

F8	
HR(bpm)	mean
	SD
SBP(mmHg)	mean
	SD
DBP(mmHg)	mean
	SD
MBP(mmHg)	mean
	SD
AoF(ml/min)	mean
	SD
MBF(ml/min/100g)	mean
	SD
PmO_2(mmHg)	mean
	SD

SD: standard deviation. HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, AoF: aortic blood flow, MBF: myoca
oxygen tension. *, $P < 0.05$ vs. respective control. #, $P < 0.05$ vs. MBF control value in F4. †, $P < 0.05$ vs. PmO_2 control values in F2 and F4.