

Title: INFLUENCE OF CONVERTING ENZYME INHIBITION ON ISOFLURANE HYPOTENSION IN DOGS

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**Introduction.** In dogs high isoflurane (ISO) concentrations (3 %) induce a marked decrease of mean arterial pressure (MAP), due to a reduction of systemic vascular resistance (SVR) and cardiac output (CO)<sup>1</sup>. Because hypotension activates the sympathetic and renin-angiotensin system (RAS), which can counteract the hypotensive effects of isoflurane, it can be expected that the same magnitude of hypotension could be obtained with a lower ISO concentration after inhibition of the angiotensin (AII) formation. The aim of the study was to compare the effect of an ISO induced hypotension on the cardiovascular system and the RAS in dogs pretreated or not with the angiotensin converting enzyme (ACE) inhibitor enalaprilat (ENAL), the biologically active metabolite of enalapril.

**Methods.** Twelve mongrel dogs (28±1 kg) were randomly divided in 2 groups: group ISO (n=6) and group ISO + ENAL (n=6). One hour after premedication with diazepam (1 mg.kg<sup>-1</sup>), anesthesia was induced with thiopental (15 mg.kg<sup>-1</sup> IV), fentanyl (30 mcg.kg<sup>-1</sup> IV) and succinylcholine (3 mg.kg<sup>-1</sup> IV) and maintained with droperidol (0.5 mg.kg<sup>-1</sup> IV), fentanyl (6 mcg.kg<sup>-1</sup>.h<sup>-1</sup>) and a O<sub>2</sub>/N<sub>2</sub>O mixture (33 % / 67 %). The following assessments were made: MAP, CO (thermodilution), HR (heart rate), SVR, CVP (central venous pressure), SV (stroke volume), PRA (plasma renin activity), ACEA (ACE-activity), AII concentration and blood gases. ENAL (0.1 mg.kg<sup>-1</sup>) was injected IV 1 hour before the ISO hypotension, which was maintained for 1 hour at 50 mm Hg. Thereafter ISO and N<sub>2</sub>O were discontinued, while the fentanyl infusion was maintained. Measurements were made at: 1. stable anesthesia 90 min prior to hypotension (= control); 2. 15 min after ENAL injection in the ISO + ENAL group; 3. during the stable hypotension; 4. 60 min after hypotension. Values were analysed by Friedman two way analysis of variance by ranks for overall differences and subsequently by the Wilcoxon matched-pairs signed-ranks test (significance was set at p < 0.05).

**Results** (see Table). The decrease of AII after ENAL resulted in a decrease of SVR and MAP with an increase of CO and CV. In the ISO group, hypotension resulted in an increase of AII, but in the ISO + ENAL group this increase was inhibited. In the ISO group MAP of 50 mm Hg was reached with an ISO concentration of 2.2 ± 0.1 % and resulted from a decrease of SVR and of CO and SV. In the ISO + ENAL group the same hypotension was obtained with only 1.0 ± 0.2 % ISO and was due to a further

decrease of SVR, while CO and SV were maintained at control levels.

**Discussion.** The study clearly indicates that the increase of AII concentration during controlled ISO hypotension is one of the major factors which counteract the direct effects of ISO on the cardiovascular system, requiring high ISO concentrations which result in a more pronounced myocardial depression so that SV and CO are reduced. Inhibition of AII formation by administration of ENAL reduces the required ISO concentration and hence the myocardial depression so that SV and CO are preserved.

PARAMETERS	CONTROL	ENAL	HYPOT	POSTHYPOT.
PRA ISO	9.4±4.4		29.4±9.7*	17.7±4.1*
ng.ml <sup>-1</sup> .h <sup>-1</sup>				
ISO+ENAL	7.4±1.8	15.2±5.4*	41.3±7.9*	15.8±3.4*
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ACEA ISO	176±21		151±27	168±27
U.l <sup>-1</sup> .min <sup>-1</sup>				
ISO+ENAL	185±19	8±2**	8±2**	11±2**
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AII ISO	77±10		313±63*	217±63*
pg.ml <sup>-1</sup>				
ISO+ENAL	108±35	31±7**	102±17	42±8**
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MAP ISO	117±8		50±1**	116±5
mm Hg				
ISO+ENAL	107±5	92±6*	50±0**	103±7
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HR ISO	116±10		121±14	117±16
beats.min <sup>-1</sup>				
ISO+ENAL	127±25	104±19	116±10	116±22
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CO ISO	2.8±0.5		1.5±0.1*	3.2±0.1
l.min <sup>-1</sup>				
ISO+ENAL	2.1±0.2	2.9±0.3*	2.0±0.2	2.9±0.2*
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SV ISO	23±4		14±2*	30±5
ml/beat				
ISO+ENAL	19±4	31±5*	18±2	29±7*
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SVR ISO	3784±798		2043±222**	2727±209
dyn.s.cm <sup>-5</sup>				
ISO+ENAL	4118±433	2632±409*	1809±156**	2762±267**
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CVP ISO	6.4±1.4		10.1±3.9	5.5±1.3
mm Hg				
ISO+ENAL	4.2±1.4	4.2±0.9	4.6±0.9	3.8±1.3
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pH ISO	7.36±0.03		7.31±0.02	7.24±0.00
ISO+ENAL	7.37±0.02	7.33±0.01	7.32±0.01	7.30±0.02

Values are means ± SEM

\* = p < 0.05 and \*\* = p < 0.01 versus control

#### Reference

- Merin RG and Basch S: Anesthesiology 55: 398-408, 1981.