ハセロン麻酔下の犬におけるDopamineの不整脈誘発性及び血行動態に及ぼす影響について

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Arrhythmogenicity of Dopamine and its Effects on Hemodynamics in Dogs under Halothane Anesthesia

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ABSTRACT. The arrhythmogenicity of dopamine, its effects on cardiac function, hemodynamics, and diuresis under halothane anesthesia were evaluated in dogs. The induction time of arrhythemias and the effect of arrhythmias on cardiac function, hemodynamics, and diuresis were determined after infusion of dopamine for 30-min period at increasing doses of 3, 5, 7, 10, and 15 μg/kg/min. The results were as follows. 1. Arrhythmia induction percentage was 28.6% at 5 μg/kg/min, 42.9% at 7 μg/kg/min, 25% at 10 μg/kg/min, and 41.7% at 15 μg/kg/min. The induction time of arrhythemias (sec) was 459 at 5 μg/kg/min, 332 at 7 μg/kg/min, 152 at 10 μg/kg/min, and 279 at 15 μg/kg/min. No arrhythmias were present at 3 μg/kg/min. 2. Heart rate and myocardial oxygen consumption was increased in the arrhythmia-induced group compared to the non-arrhythmia-induced group. 3. Myocardial contractility, mean aortic pressure, mean pulmonary arterial pressure, and diuresis increased dose-dependently in the non-arrhythmia-induced group; however, these measures were increased in the arrhythmia-induced group without regard to dose.—KEY WORDS: arrhythmogenicity, dog, dopamine, halothane, hemodynamics.

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Dopamine is a catecholamine currently used in the management heart failure. Numerous studies on the cardiovascular and hemodynamic effects of dopamine have been reported [2, 3, 5, 19, 23]. It is well recognized that administration of epinephrine increases the development of arrhythmia under the influence of inhalation anesthetic agents such as halothane [7, 8, 11, 12, 17].

Studies of the arrhythmogenicity of dopamine have been conducted by infusion of very high dose of dopamine that far exceed clinical doses [1, 6]. However the arrhythmogenicity of low dose dopamine infusions, which are clinically applicable, have not been yet studied. Since halothane is still a major inhalation anesthetic agent in veterinary practice, interactions between low dose dopamine and halothane need to be studied. Hence, the purposed of this study were to investigate the arrhythmogenicity of dopamine infusion in a low dose infusion and the cardiovascular and hemodynamic differences between the arrhythmia-induced group and non-arrhythmia-induced group under halothane anesthesia.

MATERIALS AND METHODS

Fourteen healthy mongrel dogs of either sex, weithing 9 to 26 kg were anesthetized with an intravenous injection of sodium pentobarbital (25 mg/kg body weight) and following endtracheal intubation the dogs wer ventilated with 1% to 1.5% halothane, volatilized by a precision vaporizer (Fluotec 3, BOC).

A femoral arterial catheter was placed for blood sampling to evaluate acid-base status and for monitoring of intraarterial pressure. Arterial blood-gas analysis were carried out

to maintain PaCO2 at 35 to 40 mmHg using a volume-limited ventilator (Servovent MS 2000, Manlay). When necessary, bicarbonate was admininistered to maintain a PH between 7.35 and 7.40. A femoral vein was cannulated for administration of fluid and drugs. Left ventricular pressure and left ventricular dp/dt (LV dp/dt) were measured using a 7F catheter positioned in the left ventricle. Mean pulmonary arterial pressure, mean pulmonary arterial wedge pressure, and central venous pressure were measured using a Swan-Ganz thermodilution catheter (TC-704, Gould H. B.) positioned in the pulmonary artery via the external juglar vein. Pressures were measured with pressure transducers (SCK-590, Gould H. B.) connected to a polygraph (Nihon Koden). Cardiac output measurements were made, using a cardiac output computer (MTC-6100, Nihon Koden). Recordings of heart rate and rhythm were derived from a lead 11 ECG. By abdominal lapatomy, an electromagnetic flowmeter (MVF-3200, Nihon Koden) was positioned around the renal artery to measure renal arterial blood flow. Urine was collected before and after dopamine infusion from a catheter positioned in the bladder. Urine output was caluculated by dividing urine volume during each half hour period of dopamine infusion by 30 min. Lactate Ringer's solution was infused at a rate of 10 m*l*/kg/hr during the experimental period. Twelve mg of dopamine was diluted in 50 m*l* of 5% glucose solution.

After achieving steady state, each dog was infused in order with dopamine (Inoban, Kyowa Hatukou) at 3, 5, 7, 10 and 15 μg/kg/min each for 30 min utilizing syringe pump (STC-521, TERUMO Co. LTD) with a 30 min recovery period between each dose. The time When four or more ventricular premature complexs were produced within 15 sec of dopmaine infusion was considered as arrhythemia induction time [9].

Double product was caluculated as LVP×HR and used as an index of myocardial oxygen consumption [10, 24]. Data obtained from these measurements were standardized by percent change and analyzed to compare the non-arrhythmia-induced group with the arrhythmia-induced group, by paired Student's T-test.

RESULTS

A representative trace of electrocardiogram (ECG), arterial pressure (SAP), pulmonary arterial pressure (PAP), central venous pressure (CVP), left ventricular pressure (LVP), left ventrcular dp/dt (LVdp/dt), and renal blood flow (RBF) during 7, 10, and 15 μg/kg/min dopamine infusion period under halothane anesthesia in dog is represented in Fig. 1. Ventricular arrhythmias were present in 4 of 14 dogs 828.6%) at 5 μg/kg/min, 6 of 14 dogs (42.9%) at 7 μg/kg/min, 3 of 12 dogs (25%) at 10 μg/kg/min, and 5 of 12 dogs (41.2%) at 15 μg/kg/min after a 30-min infusion period. Two dogs of the 14 dogs were eliminated from the study due to the development of metabolic acidosis. The mean arrhythmia induction time (mean±SD) were 459±274 at 5 μg/kg/min, 332±253 at 7 μg/kg/min, 152±55 at 10 μg/kg/min (Fig. 2).

The effects of dopamine on heart rate, double product, and LVdp/dt are shown in Fig 3. In the non-arrhythmia-induced group, heart rate slightly increased in comparison with the control values from 3 to 7 μg/kg/min of dopamine infusion, but increased to 38.9% over control values at 15 μg/kg/min. A dose-dependent increase in heart rate were observed: it increased significantly to 45.1% at 7 μg/kg/min ($p<0.05$), 62.3% at 10 μg/kg/min ($p<0.01$), and 82.1% at 15 μg/kg/min ($p<0.005$) in the arrhythmia-induced group from control values. Double product increased significantly to 105.4% at 7 μg/kg/

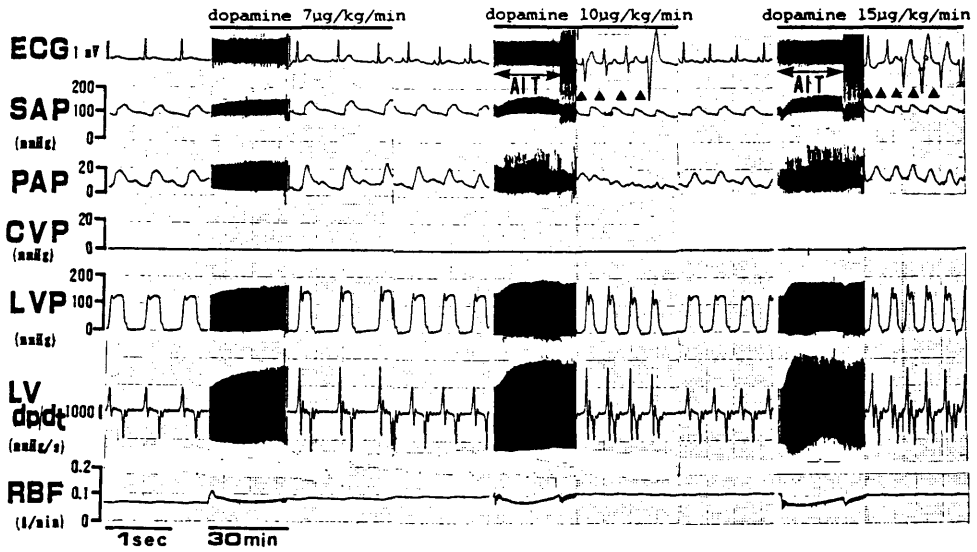

Fig. 1. A representative trace of electrocardiogram (ECG), arterial pressure (SAP), pulmonary arterial pressure (PAP), central venous pressure (CVP), left ventricular pressure (LVP), left ventrcular dp/dt (LVdp/dt), and renal blood flow (RBF) during 7, 10, and 15 μg/kg/min dopamine infusion period under halothane anesthesia in a dog. Black allows indicate ventricular arrhythmias. Arryhthmia induction time (AIT) indicates the time when four or more ventricular premature complexes were produced within 15 sec after the onset of dopamine infusion.

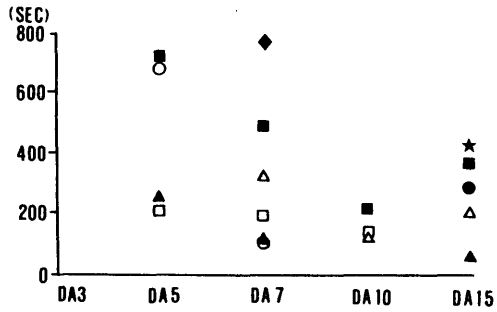

Fig. 2. Arrhythmia induction times (AIT, sec) during dopamine infusion. Arrhythmias were present in 4 dogs (■, □, ▲, ○) at 5 μg/kg/min (DA5), 6 dogs (■, □, ▲, △, ○, ◆) at 7 μg/kg/min (DA7), 3 dogs (■, □, △) at 10 μg/kg/min (DA10), and 5 dogs (■, ▲, △, ●, ★) at 15 μg/kg/min (DA15) after a 30-min infusion period. No arrhythmias were present at 3 μg/kg/min (DA3).

min ($p<0.005$), 125.5% at 10 μg/kg/min ($p<0.01$), and 129.1% at 15 μg/kg/min ($p<0.01$) in the arrhythmia-induced group and 171.5% at 15 μg/kg/min ($p<0.01$) in the non-arrhythmia-induced group.

LVdp/dt increased significantly to 105% at 7 μg/kg/min ($p<0.01$), 102.1% at 10 μg/kg/min ($p<0.01$), and 82.3% at 15 μg/kg/min ($p<0.01$) in the arrhythmia-induced group, and 172.6% at 15 μg/kg/min ($p<0.01$) in the non-arrhythmia-induced group. LVdp/dt increased dose-dependently in the non-arrhythmia-induced group (Fig. 3).

Mean arterial pressure increased dose-dependently to 6.3% at 5 μg/kg/min, 15.7% at 7 μg/kg/min, 26.9% at 10 μg/kg/min, and 40% at 15 μg/kg/min in the non-arrhythmia-induced group, but not in the arrhythmia-induced group (Fig. 4). Significant differences between two groups were not observed in the mean arterial pressure.

Mean pulmonary arterial pressure increased dose-dependently at 7 (11.3%), 10 (26.2%), and 15 (47%) μg/kg/min in the non-arrhythmia-induced group and increased significantly at 15 μg/kg/min (128%) in the arrhythmia-induced group (Fig. 4). Mean pulmonary arterial wedge pressure

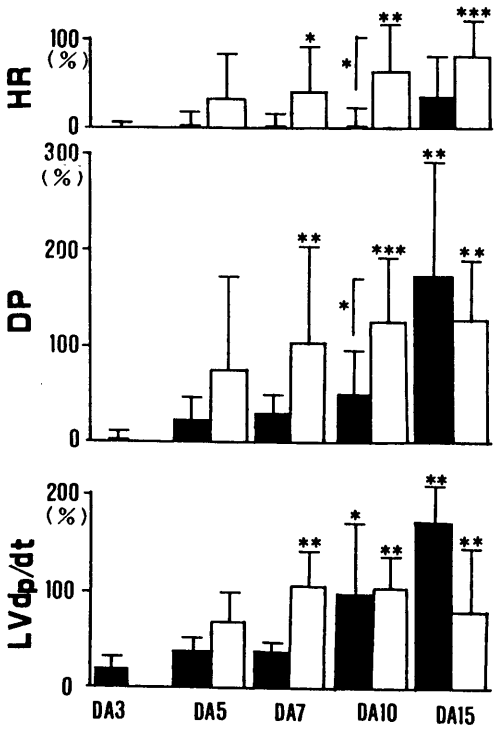

Fig. 3. Effects of 30-min dopamine infusion on heart rate (HR), double product (DP), and left ventricular dp/dt (LVdp/dt). Black column=Percent changes of non-arrhythmia-induced group (mean+SD); white column=Percent changes of arrhythmia-induced group (mean+SD); white column=Percent changes of arrhythmia-induced group (mean+SD); DA3, DA5, DA , DA10, and DA15=30 min after infusion of 3, 5, 7, 10, and 15 μg/kg/min of dopamine respectively; *Significant difference from control (P<0.05), **(P<0.01), ***(P<0.001).

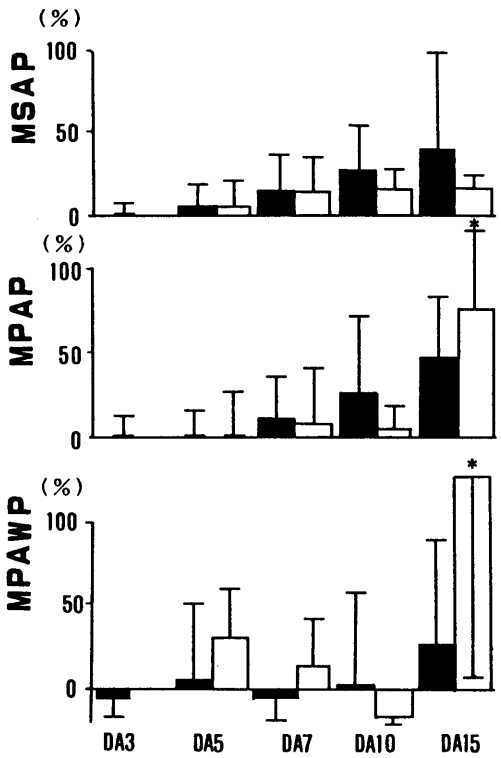

Fig. 4. Effects of 30-min dopamine infusion on mean arterial pressure (MSAP), mean pulmonary arterial pressure (MPAP), and mean pulmonary arterial wedge pressure (MPAWP). Black column=Percent changes of non-arrhythmia-induced group (mean+SD); white column=Percent changes of arrhythmia-incuced group (mean+SD); DA3, DA5, DA7, DA10, and DA15=30 min after infusion of 3, 5, 7, 10, and 15μg/kg/min of dopamine respectively; *Significant difference from control (P<0.05).

was variable and not significantly at 15 μg/kg/min in the arrhythmia-induced group (Fig. 4).

Cardiac output increased at all five doses, but dose-dependent and significant changes were not seen in both groups (Fig. 5). Renal blood flow increased at all doses in both groups, especially increased to 62.2% at 15 μg/kg/min in the non-arrhythmia-induced group (Fig. 5).

Urine output increased dose-dependently to 58.6% at 3 μg/kg/min, 142.3% at 5 μg/kg/min (p<0.01), 261.5% at 7 μg/kg/min (p<0.01), 302.7% at 10 μg/kg/min (p<0.05), and 395.8% at 15 μg/kg/min (p<0.01) in the non-arrhythmia-induced group (Fig. 6). Dose-dependent increase were not seen in the arrhythmia-induced group, but significant changes were seen at 7 μg/kg/min (563.7%, p<0.01) and 15 μg/kg/min (341.2%, p<0.01) in the arrhythmia-induced group.

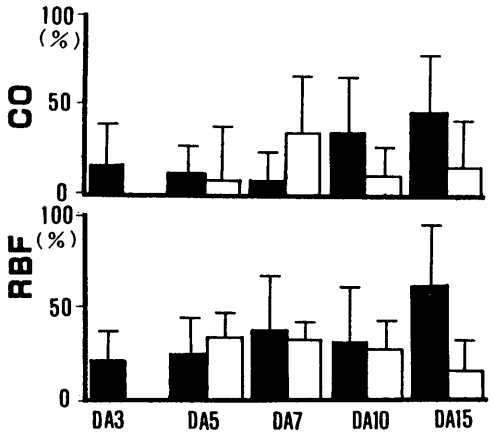

Fig. 5. Effects of 30-min dopamine infusion on cardiac output (CO) and renal blood flow (RBF). Black column=Percent changes of non-arrhythmia-induced group (mean=SD); white column=Percent changes of arrhythmia-induced group (mean+SD); DA3, DA5, DA7, DA10, and DA15=30 min after infusion of 3, 5, 7, 10, and 15 μg/kg/min of dopamine respectively.

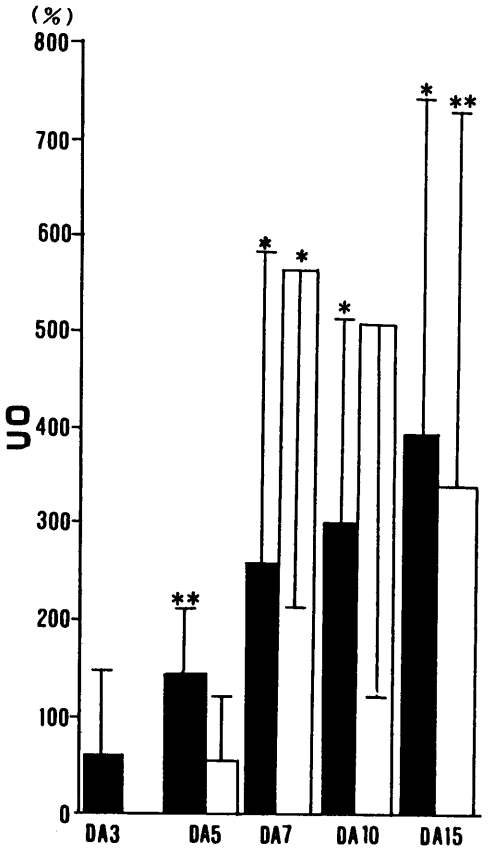

Fig. 6. Effects of 30-min dopamine infusion on urine output (UO). Black column=Percent changes of non-arrhythmia-induced group (mean+SD); white column=percent changes of arrhythmia-induced group (mean+SD); DA3, DA5, DA7, DA10, and DA15=30 min after infusion of 3, 5, 7, 10, and 15 μg/kg/min of dopamine respectively; *Significant difference from control ($P<0.05$), ** ($P<0.01$), *** ($P<0.001$).

DISCUSSION

In veterinary medicine, dopamine has been used to control circulatory failure or myocardial failure caused by excessive administration of anesthetic drugs because of its superior cardiovascular effects [14, 15, 20].

Halothane induces electrophysiologic alterations within Purkinje fibers and myocardial tissues such that ventricular arrhythmogenesis mediated through adrenergic mechanisms is markedly enhanced [21]. The arrhythmogenic sensitizing action of halothane to epinephrine is considered to be linked to alpha-adrenergic receptor activation [16, 22]. The mean arterial pressure increased dose dependently with dopamine administration above 5 μg/kg/min, and arrhythmias appeared; however, at the lower dose of 3 μg/kg/min, mean arterial pressure did not decrease. Thus the increase in the mean arterial pressure which is closely related to alpha-adrenergic receptor activation may cause of genesis of arrhythmia. Alteration in blood pressure and heat rate may alter the arrhythmogenic actions of epinephrine [6].

Mean pulmonary arterial pressure and mean pulmonary arterial wedge pressure increased at 15 μg/kg/min infusion in both groups indicating pulmonary vascular vasoconstriction [13]. Hence, it may be recommended to avoid dopamine infusion in dogs with higher pulmonary arterial pressures, such as Dirofilaria immitis infected dogs,

because pulmonary hypertension in these dogs may worsen with dopamine therapy and lead to acute right heat failure.

Urine output increased more markedly than cardiac output and renal blood flow. This may have occurred not only as a result of renal arterial dilatation and increases in cardiac output and renal blood flow, but also as a result of other mechanisms such as sodium diuresis [4] and intrarenal blood flow redistribution [18]. Therefore, we were able to confirm a significant effect of dopamine on diuresis over the entire range of doses of dopamine administration regardless the presence of arrhythmias.

In conlusion, fatal arrhythmias were not produced by dopamine infusion under the influence of halothane anesthesia, though, ventricular premature complexes appeared during low-dose of 3 μg/kg/min dopamine infusion. Tendency toward arrhythmias increased with the increase in a dose of dopamine infused, and myocardial oxygen consumption increased.

Pulmonary vasoconstriction occurred at higher doses of dopamine infusion. Attention should be given to cardiovascular monitoring in order to avoid undesirable side effects such as arrhythmias and vasoconstriction, including pulmonary vasoconstriction, when using dopamine in the treatment of heart failure.

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要　　約

ハセロン麻酔下の犬における Dopamine の不整脈誘発性及び血行動態に及ぼす影響について：佐藤　隆・鷲巣　誠・小林圀仁・三阪和徳・林　太郎・織間博光・本好茂一（日本獣医畜産大学家畜病院）——ハセロン吸入麻酔下の犬に Dopamine 3～15μg/kg/min の臨床薬用量を30分間投与し，不整脈誘発性，血行動態及び利尿効果について用量依存性の変化の有無並びに不整脈の有無による変化の差について検討した結果以下の成績を得た．1）不整脈出現率は用量依存性に増大した．また，用量に関わらず投与時間の延長に伴い不整脈の発生を見た．2）心拍数及び心筋酸素消費量の指標である double-product は，不整脈出現群で用量依存性に増大し，不整脈出現群の増加の程度をいずれも上回った．3）心収縮力は，両群ともに用量依存性に増大した．4）肺血行動態に関しては，15μg/kg/min で血圧の上昇を見た以外は用量増大に伴う一定の変化は観察されなかった．5）利尿効果は，両群ともに用量依存性の変化を示した．以上からハロセン麻酔下に於ける Dopamine 投与に際しては，投与時間の延長に伴う不整脈誘発性及び高用量での肺血行動態に注意を払う必要がある．