Effects of Denopamine (TA-064), a New Positive Inotropic Agent, on Myocardial Oxygen Consumption and Left Ventricular Dimension in Anesthetized Dogs

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Abstract—We compared the effects of denopamine (TA-064) and isoproterenol on hemodynamics, myocardial oxygen consumption and the left ventricular (LV) dimension in halothane-N₂O anesthetized dogs. Denopamine (0.25–1 μg/kg/min, i.v., infusion × 15 min) produced a maximum increase in LV dp/dt max by 64% of the control, without affecting aortic pressure significantly. Doses of isoproterenol (0.01–0.04 μg/kg/min, i.v., infusion × 15 min) were selected to produce a positive inotropic action similar to that of denopamine. Denopamine produced significantly less increasing effects in heart rate, cardiac output and myocardial oxygen consumption and had more reducing effects in LV internal diameter than isoproterenol, while isoproterenol tended to produce a more potent increase in coronary blood flow, but a smaller decrease in LV end-diastolic pressure than denopamine. PQ interval was similarly reduced. Denopamine caused no substantial increase in myocardial oxygen consumption at a lower dose, at which LV dp/dt max was significantly increased. A weak effect of denopamine on myocardial oxygen consumption may result partly from a weak positive chronotropic effect and partly from a reduction of preload and cardiac size.

Denopamine ((−)-(R)-1-(p-hydroxy-phenyl)-2-((3,4-dimethoxyphenethyl)-amino)ethanol, TA-064) is a newly synthesized positive inotropic agent which is orally active and long acting (1). The positive inotropic action of denopamine has been observed in open-chest animals (2), in chronically instrumented dogs (3) and in humans as well (4). Although denopamine has a selective β₁-adrenoceptor agonistic property (2, 5), it has been shown to produce a weak increasing effect on heart rate and little effect on systemic blood pressure in conscious and anesthetized dogs (1–3).

It has been reported that acetylstrophanthidin increased myocardial oxygen consumption (MVO₂) in the normal heart, while it has no effect on MVO₂ in the preparation in which left ventricular end-diastolic pressure (LVEDP) was elevated (6). This has been interpreted as a reduction of cardiac size, resulting in a reduction of ventricular wall tension that tends to oppose an increase in MVO₂.

We were interested in the effects of denopamine on MVO₂ with a special reference to the left ventricular (LV) internal diameter, because wall tension is dependent on cardiac size. In the present study, we examined the effects of denopamine on hemodynamics, LV function, coronary circulation, MVO₂ and LV internal diameter, and the effects were compared with those of isoproterenol.

Materials and Methods

Male mongrel dogs weighing 18 to 25 kg were used. Anesthesia was initiated with ketamine hydrochloride, 30 mg/kg, i.v. After orotracheal intubation, respiration was controlled by an anesthesia ventilator (FO-20, Acoma Ikakogyo). About one percent halothane was delivered from a calibrated vaporizer in 70–80% nitrous oxide: 30–20%
oxygen. Respiration volume was adjusted to establish physiological blood gas partial pressure and acidity. Body temperature was kept constant throughout the experiment by a heating pad.

Aortic blood pressure was measured by a pressure transducer (MPU-0.5, Nihon Kohden) connected to a catheter indwelled into the thoracic aorta via the femoral artery. Heart rate was measured by a cardiograph, triggered by ECG (lead II). After median sternotomy, aortic flow and coronary blood flow were measured with an electromagnetic flowmeter (MF-27, Nihon Kohden) whose flow probes (Nihon Kohden) were attached to the root of the aorta and the circumflex branch, respectively. Aortic flow was regarded as cardiac output. Stroke volume and total peripheral resistance were obtained by dividing aortic flow by heart rate and dividing mean blood pressure by aortic flow, respectively. A calibrated micro-manometer (Konigsberg, P4.5) was implanted within the LV chamber through the apex, and the first derivative of LV pressure (LV dp/dt) was measured by an analogue differentiator (EQ-600G, Nihon Kohden). LV dp/dtmax and dp/dt/P40 were obtained to evaluate the contractile state. The latter has been demonstrated to be relatively insensitive to variations in preload and afterload (7, 8).

For measuring the LV internal diameter, an ultrasonic dimension gauge (Schuessler and Associate) was used. A pair of ultrasonic crystals was implanted within the lumen of the left ventricle so that they face each other across the internal minor axis. Simultaneous changes of thickness of the LV anterior wall were also measured with a pair of the ultrasonic crystals. These parameters were recorded on a multichannel recorder (WT-685G, Nihon Kohden).

Polyvinyl tubings were inserted into great cardiac vein and femoral artery to get coronary venous and arterial blood samples, respectively. Blood was withdrawn anaerobically into preheparinized syringes and analyzed for PO2, PCO2 and pH with a blood gas analyzer (PHM 72 MK 2, Radiometer) and for oxygen saturation and hemoglobin with a hemoximeter (OSM 2, Radiometer). The blood oxygen content was obtained indirectly from oxygen saturation and hemoglobin. The oxygen consumption was calculated as the product of coronary blood flow and coronary arterio-venous (A-V) O2 difference. The region perfused with the circumflex branch of the left coronary artery was identified by staining with Evans blue dye.

Denopamine (Tanabe) (dissolved in the corresponding amount of HCl and diluted with 0.9% NaCl solution) and (±)-isoproterenol hydrochloride (Kaken Kagaku) were used. Isoproterenol (0.01, 0.02 and 0.04 μg/kg/min) was infused cumulatively into the femoral vein for 15 min for each dose and then denopamine (0.25, 0.5 and 1 μg/kg/min) was infused similarly. At least one hour elapsed between the two drugs to permit recovery of cardiovascular variables. Doses were selected to exhibit an increase in LV dp/dtmax to a similar extent at the upper dose of each drug.

Statistical analysis: All experimental data are presented as the mean±S.E.M. The statistical significance of the differences between the control and drug treatment was determined by the paired t-test. Two-way analysis of variance was used to determine the significance of difference between denopamine-induced and isoproterenol-induced changes. The differences were considered statistically significant if P values are less than 0.05.

Results

Cardiohemodynamic effects of denopamine: Results of a typical experiment are depicted in Fig. 1, and the summarized effects are presented in Table 1. The cardiohemodynamic effects of denopamine at each dose reached the peak at 15 min of infusion. Denopamine produced an increase in LV dp/dt with a concomitant reduction in the internal diameter of the left ventricle (Fig. 1). As shown in Table 1, the increases in LV dp/dtmax and LV dp/dt/P40 at a rate of 1 μg/kg/min were 64% and 43%, respectively. At the same time, heart rate was increased, but to a lesser extent compared with LV dp/dtmax. Aortic pressure was not changed significantly. Cardiac output was increased and LVEDP was decreased. These effects
were nearly dose-dependent. Total peripheral resistance fell and systolic LV pressure rose significantly at the upper dose. Stroke volume was not increased significantly.

Cardiohemodynamic effects of isoproterenol: The effects of isoproterenol on cardiohemodynamic variables are shown in Table 2. The peak responses were obtained within 10 min of infusion at each dose. The effects of isoproterenol were qualitatively similar to those of denopamine, but the actions in some variables were quantitatively different. Isoproterenol produced an increase in LV dp/dt max to a similar extent to that of denopamine, while isoproterenol increased heart rate and cardiac output to a significantly greater extent than denopamine. Isoproterenol tended to cause a more marked reduction in total peripheral resistance than denopamine, whereas the decrease in LVEDP was small and not significant. In spite of a marked increase in cardiac output, isoproterenol did not increase stroke volume significantly.

Effects on ECG: Parameters in ECG are shown in Table 3. Denopamine produced a reduction in PQ and QT intervals and the amplitude of R wave, while the QRS interval was not changed. The effect of isoproterenol on ECG was similar to that of denopamine. The effects of the two drugs were not significantly different from each other.

Effects on myocardial oxygen consumption: Table 4 shows the effects of denopamine and isoproterenol on MVO2. Denopamine produced no significant effects on oxygen saturation in arterial and coronary venous blood. Denopamine exhibited a significant increase in coronary blood flow at the middle and upper doses, and MVO2 tended to increase. Isoproterenol showed a significantly greater increase in MVO2 and tended to increase coronary blood flow more than denopamine. In contrast to denopamine, A-V O2 difference with isoproterenol tended to increase, and oxygen saturation in arterial and coronary venous blood tended to decrease.

Figure 2 illustrates the correlation between the increase in LV dp/dt max and in MVO2.
Table 1. The effects of dopamine on hemodynamics in the anesthetized dog (n=6)

| Variable                                | Control     | 0.25        | 0.5         | 1           | J%  |
|-----------------------------------------|-------------|-------------|-------------|-------------|-----|
| Aortic systolic pressure (mmHg)         | 113±6.2     | 114±6.1     | 118±6.3     | 119±7.6     | +6  |
| Aortic diastolic pressure (mmHg)        | 74±4.9      | 74±5.2      | 77±5.3      | 77±6.1      | +5  |
| Mean aortic pressure (mmHg)             | 89±6.1      | 90±6.5      | 93±6.3      | 92±6.5      | +3  |
| Heart rate (beats/min)                  | 136±7.1     | 142±7.8*    | 152±8.8**   | 165±11.4**  | +21# |
| LV dp/dtmax (mmHg/sec)                  | 1740±223    | 2030±253**  | 2350±326**  | 2870±440**  | +64 |
| LV dp/dt/Pa (sec⁻¹)                     | 43±6.1      | 47±6.8**    | 52±7.0**    | 61±8.9**    | +43 |
| LV systolic pressure (mmHg)             | 108±7.0     | 109±7.1     | 113±8.2     | 115±8.1*    | +7  |
| LV end-diastolic pressure (mmHg)        | 2.5±0.32    | 1.7±0.43*   | 1.3±0.52*   | 1.2±0.67*   | −57 |
| Cardiac output (ml/min)                 | 1320±126    | 1420±115    | 1520±116*   | 1620±124**  | +24#|
| Stroke volume (ml)                      | 9.9±1.26    | 10.2±1.09   | 10.2±1.01   | 10.0±0.95   | +4  |
| Total peripheral resistance (mmHg/l/min)| 71±8.3      | 66±5.8      | 64±5.1      | 58±5.1*     | −16 |

*P<0.05, **P<0.01 versus control (paired t-test). #P<0.05, ##P<0.01: indicating the significance of difference between dopamine-induced and isoproterenol-induced changes by two-way analysis of variance.
Table 2. The effects of isoproterenol on hemodynamics in the anesthetized dog (n=6)

| Variable                              | Control       | 0.01          | During isoproterenol infusion (µg/kg/min, for 15 min) | 0.02 | 0.04 |
|---------------------------------------|---------------|---------------|------------------------------------------------------|------|------|
|                                       |               | %             |                                                      |      |      |
| Aortic systolic pressure (mmHg)       | 109±7.0       | 111±8.4       |                                                      | +1   | +2   |
| Aortic diastolic pressure (mmHg)      | 73±4.6        | 72±4.6        |                                                      | -1   | -0.1 |
| Mean aortic pressure (mmHg)           | 87±5.5        | 87±5.9        |                                                      | +0.4 | +3   |
| Heart rate (beats/min)                | 133±6.5       | 148±7.2**     |                                                      | +12  | +21  |
| LV dp/dt_{max} (mmHg/sec)             | 1770±218      | 2120±225**    |                                                      | +21  | +40  |
| LV dp/dt/p_{ao} (sec^{-1})            | 43±5.3        | 47±6.0*       |                                                      | +10  | +32  |
| LV systolic pressure (mmHg)           | 107±6.8       | 112±5.6*      |                                                      | +5   | +7   |
| LV end-diastolic pressure (mmHg)      | 2.8±0.53      | 2.2±0.54      |                                                      | -25  | -27  |
| Cardiac output (ml/min)               | 1440±86       | 1650±111*     |                                                      | +15  | +24  |
| Stroke volume (ml)                    | 11.0±1.00     | 11.3±1.08     |                                                      | +3   | +3   |
| Total peripheral resistance (mmHg/l/min) | 62±5.2       | 55±5.4**      |                                                      | -12  | -16  |

*P<0.05, **P<0.01 versus control (paired t-test)
Table 3. The effects of dopamine and isoproterenol on electrocardiogram (lead II) in the anesthetized dog (n=6)

| Variable            | Control       | 0.25 | During dopamine infusion (μg/kg/min, for 15 min) | 0.5 | During isoproterenol infusion (μg/kg/min, for 15 min) | 0.01 | 0.02 | 0.04 |
|---------------------|---------------|------|----------------------------------------------|-----|----------------------------------------------------|------|------|------|
|                     |               |      | D%                                           |     |                                                   | D%   | D%   | D%   |
| PQ interval (msec)   | 92±6.1        | 89±6.4** | -3                                          | 84±4.7* | -8                                               | 82±4.9** | -11  |
| QRS interval (msec)  | 57±1.5        | 57±1.6 | -0.3                                         | 58±1.6 | +1                                                | 57±1.6 | +0.02|
| QT interval (msec)   | 226±10.1      | 219±9.8* | -3                                          | 212±8.3* | -6                                                 | 200±7.1** | -11  |
| R-wave amplitude (mV)| 1.25±0.149   | 1.23±0.153 | -2                                         | 1.19±0.160** | -6                                               | 1.13±0.171** | -11  |
|                     |               |      | D%                                           |     |                                                   | D%   | D%   | D%   |
| PQ interval (msec)   | 95±8.1        | 92±8.3* | -3                                          | 89±8.1* | -6                                               | 88±5.8* | -7   |
| QRS interval (msec)  | 57±1.6        | 56±1.9 | -2                                          | 57±1.8 | +0.3                                              | 57±1.7 | -1   |
| QT interval (msec)   | 226±9.9       | 218±8.6* | -3                                          | 210±9.0** | -7                                               | 202±8.0** | -11  |
| R-wave amplitude (mV)| 1.34±0.142  | 1.28±0.153* | -5                                         | 1.24±0.141** | -8                                               | 1.19±0.138* | -11  |

*P<0.05, **P<0.01 versus control (paired t-test)
### Table 4. The effects of dopamine and isoproterenol on myocardial oxygen consumption in the anesthetized dog (n=6)

| Variable                                           | Control     | 0.25       | 0.5        | 1          | 0.01       | 0.02       | 0.04       | J%        | J%        | J%        |
|----------------------------------------------------|-------------|------------|------------|------------|------------|------------|------------|-----------|-----------|-----------|
| Arterial blood oxygen % saturation                 | 91.4±2.30   | 91.7±2.28  | +0.3       | -0.1       | 91.7±2.23  | +0.3**     |            |           |           |           |
| Coronary sinus blood oxygen % saturation           | 27.7±2.92   | 28.3±3.26  | +2         | +0.1       | 28.5±3.10  | +3**       |            |           |           |           |
| Myocardial A-V oxygen difference (ml/100 ml blood) | 11.4±1.15   | 11.3±1.29  | -1         | -1         | 11.2±1.13  | -1**       |            |           |           |           |
| Left coronary arterial flow (ml/100 g LV/min)      | 74±4.3      | 76±4.4     | +3         | +9         | 85±5.8**   | +15        |            |           |           |           |
| Myocardial oxygen consumption (ml O2/100 g LV/min) | 8.2±0.51    | 8.4±0.69   | +2         | +8         | 9.3±0.84   | +14*       |            |           |           |           |
| Arterial blood oxygen % saturation                 | 92.5±2.05   | 91.9±2.03  | -1         | -2         | 90.2±2.80  | -3         |            |           |           |           |
| Coronary sinus blood oxygen % saturation           | 28.7±3.56   | 28.2±3.13  | -1         | -2         | 27.3±2.93  | -4         |            |           |           |           |
| Myocardial A-V oxygen difference (ml/100 ml blood) | 11.3±1.20   | 11.5±1.21  | +2         | +3         | 11.8±1.25  | +5         |            |           |           |           |
| Left coronary arterial flow (ml/100 g LV/min)      | 78±4.7      | 82±4.6*    | +6         | +13        | 97±3.8*    | +26        |            |           |           |           |
| Myocardial oxygen consumption (ml O2/100 g LV/min) | 8.6±0.71    | 9.2±0.71** | +8         | +16        | 11.5±1.45* | +33        |            |           |           |           |

*P<0.05, **P<0.01 versus control (paired t-test). *P<0.05, **P<0.01: indicating the significance of difference between dopamine-induced and isoproterenol-induced changes by two-way analysis of variance.
Table 5. The effects of dopamine and isoproterenol on left ventricular internal diameter and wall thickness in the anesthetized dog (n=8)

| Variable          | Control | During dopamine infusion (µg/kg/min, for 15 min) |          |          |          |          |          |
|-------------------|---------|-----------------------------------------------|---------|---------|---------|---------|
|                   |         | 0.25                                          | 0.5     | 1       | 1       |
| LV internal diameter |         |                                               |         |         |         |         |
| End-diastole (mm) | 26.0±1.60 | 24.6±1.89*                                  | -6      | 23.5±1.83** | -10     | 22.4±1.96** | -15**   |
| End-systole (mm)  | 22.2±1.69 | 20.5±1.67**                                 | -8      | 19.8±1.83** | -11     | 18.5±2.04** | -18*    |
| LV wall thickness |         |                                               |         |         |         |         |         |
| End-diastole (mm) | 9.8±0.61  | 10.2±0.67                                   | -4      | 10.5±0.71*  | +4      | 10.8±0.72*  | +9      |
| End-systole (mm)  | 11.4±0.88 | 12.0±0.93*                                  | +5      | 12.4±0.93*  | +9      | 12.9±0.94** | +14     |

| Variable          | Control | During isoproterenol infusion (µg/kg/min, for 15 min) |          |          |          |
|-------------------|---------|-----------------------------------------------|---------|---------|---------|
|                   |         | 0.01                                          | 0.02    | 0.04    |
| LV internal diameter |         |                                               |         |         |         |
| End-diastole (mm) | 26.3±1.76 | 25.2±1.87*                                  | -4      | 24.9±1.70*  | -5      | 24.0±1.80**  | -9      |
| End-systole (mm)  | 21.9±1.72 | 20.6±1.82*                                  | -6      | 20.2±1.63** | -8      | 19.2±1.78**  | -13     |
| LV wall thickness |         |                                               |         |         |         |
| End-diastole (mm) | 10.0±0.95 | 10.3±0.72                                   | -4      | 10.4±0.67*  | +4      | 10.5±0.71*  | +5      |
| End-systole (mm)  | 11.6±0.89 | 12.2±0.95*                                  | +5      | 12.6±0.91** | +9      | 13.0±0.91**  | +13     |

*P<0.05, **P<0.01 versus control (paired t-test). #P<0.05, ##P<0.01: indicating the significance of difference between dopamine-induced and isoproterenol-induced changes by two-way analysis of variance.
or in heart rate (B) produced by denopamine and isoproterenol. Denopamine showed weaker increases in MVO₂ and in heart rate than isoproterenol, while exerting a similar positive inotropic action (Fig. 2), and it increased LV dp/dtₘₐₓ at the lower dose at which no substantial increase in MVO₂ occurred (Fig. 2A, Table 4).

Effects on left ventricular dimension: Effects of denopamine and isoproterenol on the LV internal diameter and the LV wall thickness of the left ventricle are shown in Table 5, and also in Fig. 1 for denopamine. The drugs caused a dose-dependent reduction in both LV end-diastolic and end-systolic internal diameters, with a simultaneous increase in the LV wall thickness. However, denopamine produced a significantly greater reduction in LV internal diameter than isoproterenol at the dose which produced a positive inotropic action of similar magnitude.

Discussion

Cardiovascular effects of denopamine known with bolus injection were confirmed in the present study in which denopamine was infused intravenously; i.e., an increase in contractility of the heart, weak positive chronotropic action and no substantial effects on systemic blood pressure. Isoproterenol also produced no significant effect on blood pressure, but showed greater changes in cardiac output and total peripheral resistance than denopamine, reflecting different effects between both drugs on peripheral vascular beds. Isoproterenol also produced a more potent increasing effect on heart rate than denopamine.

Positive inotropic effects of denopamine and isoproterenol as assessed by the rate of the left ventricular pressure changes were almost identical, but when positive inotropic effects were assessed by another indices, i.e., reduction in LVEDP and cardiac size, the effects of denopamine were greater than those of isoproterenol. The increase in heart rate could lead to an increase in LV dp/dt (9, 10) and to reduction in LVEDP and cardiac size. In this connection, isoproterenol, which produced marked positive chronotropic action, should have more pronounced effects in LV dp/dt, LVEDP and cardiac size than denopamine. Therefore, the reduction of preload is a characteristic feature of denopamine in the present study.

Denopamine produced a dose-related increase in LV dp/dtₘₐₓ, accompanied by an increase in MVO₂. It is of interest to note that the increase in MVO₂ with denopamine was smaller than that with isoproterenol, in spite of identical increasing effects on LV dp/dtₘₐₓ. This could be mainly explained by the weak positive chronotropic action of denopamine. However, denopamine caused no substantial increase in MVO₂ at the lower dose, while LV dp/dtₘₐₓ was increased significantly. It has been shown that a factor affecting MVO₂ other than heart rate and contractility is ventricular wall tension (11–14), and a reduction of the cardiac size has been shown to reduce MVO₂ via a reduction of wall tension. Moreover, Suga et al. (15, 16) have reported a good correlation between MVO₂ and systolic pressure-volume area. In this connection, we measured directly the LV internal diameter and found that denopamine produced a reduction in LV internal diameter more potently than does isoproterenol. Those results with denopamine are consistent with a reduction in LVEDP. These findings indicate that denopamine is more effective in reducing preload than isoproterenol. These effects of denopamine tend to oppose an increase in MVO₂, thus causing a quantitative difference.
between two drugs in the effects on MVO₂. Naturally, preload is affected by venous return. There has been no report on the effect of denopamine on venous return. It has been reported, however, that the direct vascular effect of denopamine by intraarterial administration was 1/10000 of that of isoproterenol (2). Denopamine is considered to possess practically no alpha-adrenoceptor agonistic action and very weak beta₂-adrenoceptor agonistic action (2, 5). On the other hand, isoproterenol has a marked effect on the vasculature of both arterial and venous sides, and especially, it has been reported that isoproterenol caused an increase in venous return by dilating hepatic outflow vessels (17). In the present study, an increase in cardiac output and a decrease in total peripheral resistance induced by isoproterenol were greater than those induced by denopamine. Therefore, it is inferred that denopamine had less effect on venous return and caused more pronounced reduction in preload than isoproterenol.

Among the isolated canine vascular smooth muscles of various vasculature, denopamine has been reported to produce the most potent effect in the coronary artery, due to its beta₁-adrenoceptor agonistic action (5). In the present study, denopamine had a weak increasing tendency on coronary blood flow, when compared with isoproterenol, but isoproterenol, unlike denopamine, tended to increase A-V O₂ difference. This difference with denopamine may be explained partly by the direct relaxing effect on coronary vascular smooth muscle and partly by a smaller increase in MVO₂.

Denopamine reduced PQ and QT intervals, which may be a result of its beta-adrenoceptor agonistic action as reported with isoproterenol (18). However, isoproterenol and denopamine caused a reduction of the amplitude of the R wave, probably reflecting a reduction in cardiac size (19).

The findings that denopamine produced a positive inotropic action without increasing MVO₂ substantially and had a relatively weaker effect on MVO₂ than does isoproterenol are considered to be due to not only its weak positive chronotropic effect but also a reduction of preload and/or cardiac size. This suggests the possibility that denopamine is effective in reducing high preload in patients with heart failure.

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