Effect of Isosorbide Dinitrate Infusion on the Canine Left Ventricular Force-Length Relationship

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SUMMARY

Recently, the slope (E_c) of the left ventricular (LV) end-systolic force-diameter (F_{es} - D_{es}) relationship has been proposed as a new index for assessing myocardial contractility. Using this relationship, the effects of ISDN on LV myocardial contractility were evaluated in 10 healthy adult mongrel dogs. After the intravenous infusion of propranolol and atropine to produce autonomic blockade, the inferior vena cava was gradually occluded for 20 sec to decrease preload while the dogs were kept apneic. The LV diameter was measured by ultrasonic crystals and LV pressure was measured by a micromanometer. After the control measurements, the dogs received intravenous ISDN (1, 5, 10, or 50 $\mu\text{g/kg/min}$), and inferior vena caval occlusion was repeated. E_c and the extrapolated diameter intercept (D_0) of the LV F_{es} - D_{es} relationship were determined for each dog from the end-systolic data. The differences in heart rate between the control state and ISDN infusion at any dose were not statistically significant. The E_c and D_0 values also showed no significant changes with ISDN infusion (E_c : 80 ± 19 , 83 ± 20 , 84 ± 17 , 82 ± 24 , and 87 ± 24 g/cm for 0, 1, 5, 10, and 50 $\mu\text{g/kg/min}$, respectively. D_0 : 1.38 ± 0.42 , 1.38 ± 0.40 , 1.38 ± 0.38 , 1.34 ± 0.40 , and 1.36 ± 0.40 cm for 0, 1, 5, 10, and 50 $\mu\text{g/kg/min}$, respectively). These findings suggested that intravenous ISDN did not affect myocardial contractility in the normal in situ canine left ventricle. (Jpn Heart J 34: 91-101, 1993.)

Key Words:

Myocardial contractility Intact heart Cylinder model

NITRATES are commonly used for the treatment of congestive heart failure and ischemic heart disease. The effects of these drugs on the failing heart, i.e., an improvement of left ventricular (LV) pump performance and a decrease in LV filling pressure, are considered to be generated primarily by a reduction in preload.¹⁾⁻³⁾ Although some investigators have reported that nitrates improved LV contractility in patients with ischemic heart disease,^{4),5)} it is

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suspected that there was actually only an indirect effect on myocardial contractility that was mediated via the action of these drugs on the pathologic coronary arteries. Several studies have evaluated the effect of nitrates on isolated heart muscle preparations⁶⁻⁸⁾ or on the intact heart⁹⁻¹¹⁾ using conventional indices of cardiac performance. However, strictly speaking, none of them have examined the effect of nitrates on myocardial contractility in the intact heart.

We have recently proposed a new model (Fig. 1) for the evaluation of myocardial contractility in the intact left ventricle,¹²⁾ and the validity of this model has been confirmed by experiments in dogs¹³⁾ and humans.¹⁴⁾ The purpose of this study was to confirm that isosorbide dinitrate (ISDN) has no direct positive inotropic effect on the intact normal canine heart, and to support the hypothesis that the significant effect of nitrates on congestive heart failure or ischemic heart disease is produced via their influence on the systemic, pulmonary, and coronary circulations, and not by a direct effect on the myocardium.

METHODS

Animal preparation

Ten healthy adult mongrel dogs (11.0 ± 1.0 kg) were anesthetized with intravenous pentobarbital sodium (26 mg/kg) and instrumented as described in detail elsewhere.¹³⁾ In brief, the dogs were ventilated via an endotracheal tube using positive pressure respiration. Thoracotomy was performed through the left fourth intercostal space and the pericardium was opened. After a micromanometer-tipped catheter (MPC500, Millar Instruments) was balanced in a constant-temperature water bath (37°C), it was inserted through the apex of the left ventricle and held in place by a purse-string suture. A catheter inserted into the right femoral vein served for the infusion of drugs and fluid, while another catheter was inserted into the right femoral artery for blood gas analysis. Ties were loosely placed around the inferior vena cava for use when modifying the preload. A pair of ultrasonic crystals was implanted in the LV endocardium of each dog to provide continuous measurements of the LV anterior-posterior diameter (ultrasonic dimension system model UDM-5C, MECC, Japan, Fig. 2). The stability of the conformation of the LV pressure-diameter loops was monitored with an oscilloscope during the period when the preload was being decreased.

Experimental protocol

Arterial blood gas was analyzed (model ABL4, Radiometer, Copenhagen). Arterial PO₂ and PCO₂ were respectively maintained at pressures greater than 100 mmHg and less than 40 mmHg, despite any alterations in the inspired frac-

Fig. 1. Diagram of the cylinder model of the left ventricle. F_e = end-systolic total circumferential force on the cylinder (g); F_p = external load, end-systolic total circumferential force on the cylinder (g); H_{es} = end-systolic cylinder wall thickness; l = cylinder height of 1 cm; R_{es} = end-systolic cylinder radius (cm).

Fig. 2. The micromanometer, the location of the pair of crystals used for measuring the left ventricular diameter, and the inferior vena caval occluder used for preload reduction. LV = left ventricle; RV = right ventricle.

tion of oxygen, ventilation rate, and tidal volume. Lead II of the surface electrocardiogram (ECG) was recorded. A major reflex change of autonomic tone was defined as an increase or decrease in the heart rate of greater than 10 beats/min over the course of any vena caval occlusion.¹⁵⁾ Autonomic blockade (beta-adrenergic and vagal blockade) was induced with 2 mg/kg propranolol and 0.2 mg/kg atropine i.v.^{15),16)} At least 10 min after the initiation of autonomic blockade, the inferior vena cava was gradually occluded for 20 sec while the dog was apneic until the systolic LV pressure reached 80 mmHg. Data were initially recorded during a steady-state period after occlusion to obtain the control occlusional LV pressure, ECG, and LV anterior-posterior diameter. The inferior vena cava was then released and the systolic pressure was allowed to return to the baseline level.

After the control measurements, the dogs intravenously received ISDN, 1 μ g/kg/min via an infusion pump (STC-523, Terumo, Japan), and at least 5 min were allowed to elapse before measurements were repeated. Then, inferior vena caval occlusion was performed again and the data were recorded and stored. A special ISDN infusion catheter [infusion kit for nitroglycerin (type E),

Japan Medical Supply] was used, because ISDN is only minimally absorbed by this tube. Whenever the arterial pressure became excessively low after ISDN infusion, the dogs were given appropriate intravenous fluid supplementation (Solita T3, Shimizu Pharmaceutical Co, Japan). After completion of the initial ISDN study, doses of 5, 10, and 50 $\mu\text{g}/\text{kg}/\text{min}$ were tested in the same manner. Data were simultaneously stored in a hard disk memory at 1-msec intervals by a computer system (PC9801VX, NEC, Japan). The final arterial blood gas analysis showed a $\text{PO}_2 > 90 \text{ mmHg}$ and a $\text{PCO}_2 < 45 \text{ mmHg}$. No antiarrhythmic agents were used and no arrhythmias occurred during caval occlusion. Micromanometer drift was less than 1.0 mmHg throughout the course of the study, and positions of the ultrasonic crystals were confirmed to be appropriate by necropsy.

Data analysis and theoretical background

Instantaneous LV pressure (P , mmHg) and diameter (D , cm) data recorded from several cardiac cycles during the manipulation of preload were used for the construction of LV force-diameter loops. The LV circumferential force (F) was calculated from the equation $F = P \cdot D / \pi a$.^{12),13)} Loops constructed for one dog are shown in Fig. 3 as a representative example. End-systole was defined as the upper left corner of the LV pressure-diameter loop.^{12),13),17),18)} In the present model, LV end-systolic circumferential force ($F_{\text{es}} = P_{\text{es}} \cdot D_{\text{es}} / \pi a$, where $P_{\text{es}} = \text{LV}$

Fig. 3. Effect of isosorbide dinitrate on the left ventricular (LV) end-systolic force-diameter ($F_{\text{es}}\text{-}D_{\text{es}}$) relation. Representative LV circumferential force-diameter loops in the control contractile state obtained from one dog in response to inferior vena caval occlusion. Upper left corners of loops represent the end-systolic point in each cardiac cycle. Regression lines were estimated from the data for the LV $F_{\text{es}}\text{-}D_{\text{es}}$ relation. D =diameter; F =force.

end-systolic pressure, D_{es} = LV end-systolic diameter, and a denotes the conversion factor of $0.735 \text{ mmHg} \cdot \text{g}^{-1} \cdot \text{cm}^2$) was assumed to be linearly proportional to myocardial length. Thus, LV end-systolic force (F_{es} , g) was expressed as follows:

$$F_{es} = \pi E_c \cdot (D_{es} - D_0) \quad (1)$$

where E_c denotes the slope of the LV end-systolic force-length relation (which was used as an index of LV wall performance), and D_0 is the basal LV diameter. The linear regression equation for the LV F_{es} - D_{es} relation was obtained as Equation 2:

$$F_{es} = A \cdot (D_{es} - B) \quad (2)$$

where A is the regression coefficient and B is the X-axis intercept. Finally, E_c and D_0 were derived in the following manner from Eqs. 1 and 2, respectively:

$$E_c = A / \pi \quad (3)$$

$$D_0 = B \quad (4)$$

Digital data recorded on the hard disk were processed using a computer system (PC9801VX, NEC) and software developed in our laboratory. This system allowed us to obtain force-diameter loops, determine the end-systolic point in each cardiac cycle, estimate the regression equation for the LV F_{es} - D_{es} relation (as well as the values of E_c and D_0), and draw entire curves for the LV F_{es} - D_{es} formula.

Statistical analysis

Data are expressed as the mean $\pm$ SD. The statistical significance of differences between means was assessed by Student's paired t-test. Linear regression by the least squares method was used to fit data to the LV F_{es} - D_{es} relation.

RESULTS

Table I shows the heart rate, LV end-systolic pressure (P_{es}), diameter (D_{es}), force (F_{es}), E_c , and D_0 data in the control study and after ISDN infusion. The difference in heart rate between the control study and ISDN infusion at any dose was not statistically significant, and was less than 5 beats/min in all dogs. Thus, major reflex changes of the autonomic tone acting on the heart were not noted. LV P_{es} decreased from 126 ± 21 to 91 ± 12 mmHg during the control IVC occlusion. Similarly it decreased from 125 ± 18 to 90 ± 7 mmHg during the infusion of ISDN at $1 \mu\text{g/kg/min}$ ($p < 0.01$), from 120 ± 17 to 89 ± 7 mmHg at $5 \mu\text{g/kg/min}$ ($p < 0.01$), from 118 ± 17 to 89 ± 10 mmHg at $10 \mu\text{g/kg/min}$ ($p < 0.01$), and from

Table I. Effect of Isosorbide Dinitrate Infusion on Myocardial Contractility

	Control	Infusion rate ($\mu\text{g/kg/min}$)			
		1	5	10	50
HR (bpm)	113 $\pm$ 15	115 $\pm$ 15	114 $\pm$ 16	114 $\pm$ 16	114 $\pm$ 16
P _{es} (mmHg)	126 $\pm$ 21	125 $\pm$ 18	120 $\pm$ 17*	118 $\pm$ 17	111 $\pm$ 14**
D _{es} (cm)	2.12 $\pm$ 0.56	2.07 $\pm$ 0.51	2.01 $\pm$ 0.55**	1.98 $\pm$ 0.52**	1.93 $\pm$ 0.52**
F _{es} (g)	183 $\pm$ 58	175 $\pm$ 48	166 $\pm$ 54**	161 $\pm$ 50*	147 $\pm$ 45**
E _c (g/cm)	80 $\pm$ 19	83 $\pm$ 20	84 $\pm$ 17	82 $\pm$ 24	87 $\pm$ 24
D ₀ (cm)	1.38 $\pm$ 0.42	1.38 $\pm$ 0.40	1.38 $\pm$ 0.38	1.34 $\pm$ 0.40	1.36 $\pm$ 0.40

* $p < 0.05$, ** $p < 0.01$ (control vs. isosorbide dinitrate).

D_{es} = left ventricular end-systolic diameter; D₀ = extrapolated diameter intercept of the left ventricular F_{es}-D_{es} relation; E_c = slope of the left ventricular F_{es}-D_{es} relation; F_{es} = left ventricular end-systolic force; HR = heart rate; P_{es} = left ventricular end-systolic pressure.

111 $\pm$ 14 to 83 $\pm$ 7 mmHg at 50 $\mu\text{g/kg/min}$ ($p < 0.01$). The P_{es} value before IVC occlusion was significantly lower in the 5 and 50 $\mu\text{g/kg/min}$ ISDN studies when compared with the control study. D_{es} and F_{es} were also significantly decreased in the 5, 10 and 50 $\mu\text{g/kg/min}$ ISDN studies.

In all cases, the LV F_{es}-D_{es} relation showed near linearity (Fig. 4). E_c did not change at any level of ISDN infusion in comparison with the control level [80 $\pm$ 19 vs. 83 $\pm$ 20 (1 $\mu\text{g/kg/min}$), 84 $\pm$ 17 (5 $\mu\text{g/kg/min}$), 82 $\pm$ 24 (10 $\mu\text{g/kg/min}$), and 87 $\pm$ 24 g/cm (50 $\mu\text{g/kg/min}$)]. D₀ also did not change with any of the ISDN doses infused [1.38 $\pm$ 0.42 vs. 1.38 $\pm$ 0.40 (1 $\mu\text{g/kg/min}$), 1.38 $\pm$ 0.38 (5 $\mu\text{g/kg/min}$), 1.34 $\pm$ 0.40 (10 $\mu\text{g/kg/min}$), and 1.36 $\pm$ 0.40 g/cm (50 $\mu\text{g/kg/min}$)]. Therefore, ISDN infusion did not affect the myocardial contractile state of the canine LV myocardium.

DISCUSSION

Although several contractility indices for evaluating myocardial performance, such as the ejection fraction (EF), the mean circumferential fiber shortening velocity (mVcf), and dP/dt_{max} , have been used clinically, none of these indices can accurately evaluate LV myocardial function because of the influence of preload and/or afterload. E_{max} (the slope of the LV end-systolic pressure-volume relation) appears to be an index that is independent of preload and afterload.^{17,18)} However, there is still the problem that this index depends on LV size (the end-systolic LV volume at zero pressure, V_d).¹⁹⁻²⁴⁾ We have proposed a new cylinder model for the evaluation of LV myocardial contractility,¹²⁾ and recent studies

Fig. 4. Representative LV circumferential force-diameter loops after the intravenous infusion of isosorbide dinitrate (ISDN). Broken lines indicate the LV F_{es} - D_{es} relation during the control contractility state. Solid lines are for the data obtained after the infusion of ISDN (1, 5, 10 or 50 $\mu\text{g/kg/min}$).

have indicated that E_c is a reliable index for assessing the contractility of the intact canine and human left ventricle.^{13,14} In the present study, we accordingly evaluated the effect of ISDN infusion on the LV myocardium using the E_c value.

Direct effect of nitrates on myocardial contractility

Nitrates are well known to have a strong vasodilatory effect and to decrease both preload and afterload, but investigators still disagree concerning the posi-

tive inotropic effect of these agents. Strauer²⁵⁾ reported a positive inotropic action of nitroglycerol in isolated human LV papillary muscles obtained during surgery to implant prosthetic mitral valves. Because $V_{\max}$ was significantly increased after nitroglycerol administration, he concluded that this agent directly increased the contractility of human myocardium. On the other hand, some investigators postulate that the acceleration of myocardial contractility after nitroglycerol administration is caused by a sympathetic reflex rather than a direct drug effect. Darby et al^{9,10)} suggested that the effect of nitroglycerin on myocardial contractility was due to increased sympathetic tone as a reflex response to hypotension, because myocardial contractility was increased in dogs after the intravenous infusion of nitroglycerin and this response was abolished by vagosympathectomy. Using beta-blocking agents, Wiener et al⁴⁾ have also obtained similar results. Levy⁶⁾ examined this phenomenon by studying force-frequency relationships in the isolated rabbit left atrium, and he concluded that ISDN did not alter the basic contractility mechanism. In our present study, the index E_c did not change after ISDN infusion. Accordingly, we also suggest that ISDN does not directly affect the LV myocardium.

Indirect effects of nitrates on myocardial contractility

An experimental study which examined the effects of intravenous nitroglycerin infusion on regional myocardial blood flow showed that coronary flow increased immediately after intravenous nitroglycerin infusion, but then finally decreased with a rapid reduction of aortic pressure.¹¹⁾ Vatner et al¹⁰⁾ studied the effects of intravenous nitroglycerin infusion on coronary blood flow and resistance, LV pressure and diameter, dP/dt , $(dP/dt)/P$, and the velocity of myocardial fiber shortening in conscious dogs. They concluded that intravenous nitroglycerin produced two phases of coronary dilatation, which led to an increase in coronary blood flow. The first phase was a direct effect of nitroglycerin on the coronary vessels, while the later phase was secondary coronary vasodilatation caused by reflex sympathetic activity. This coronary vasodilatation did not affect myocardial contractility. Nitroglycerin was infused as a bolus ($40 \mu\text{g}/\text{kg}$) in their experiments, whereas we used a steady infusion at $1\text{--}50 \mu\text{g}/\text{kg}/\text{min}$, but both experiments were performed under autonomic blockade. Although we did not measure or regulate coronary blood flow, the experimental results of Vatner et al¹⁰⁾ and our findings suggest that the coronary vasodilatation and the changes of coronary blood flow distribution that are associated with the decrease in preload induced by nitrates had almost no indirect effect on myocardial contractility in normal hearts. Moreover, it also appears that nitroglycerin does not directly affect myocardial contractility.

On the other hand, there are many reports that nitrates promote myocar-

dial performance in ischemic heart disease.^{4),5)} Strauer examined the hemodynamic effect after intravenous nitroglycerin infusion and he suggested significant increases in peak dP/dt , the cardiac index, and the stroke volume index.⁵⁾ Coronary blood flow and myocardial oxygen consumption were increased in association with the enhancement of ventricular performance. However, there are also some reports that nitrates can decrease myocardial contractility.^{7),8)} It has been observed that nitrates affect subendocardial and subepicardial myocardial blood flow²⁶⁾ and dilate the coronary collaterals.²⁷⁾⁻³⁰⁾ These effects may provoke the abnormal distribution of coronary and myocardial blood flow and even cause the coronary steal phenomenon.^{26),31),32)} Using the LV end-systolic force-length relation, we previously detected a patient with ischemic cardiomyopathy who showed deterioration of myocardial contractility following nitroglycerin infusion.³³⁾ This deterioration was strongly suggested to be caused by the coronary steal phenomenon, which arose due to the pharmacological effects of nitrate on the coronary vessels.

CONCLUSION

The effects of ISDN infusion on myocardial contractility in the intact left ventricle were evaluated using the LV end-systolic force-length relation in anesthetized open-chest dogs under autonomic blockade. The slope of the LV end-systolic force-length relation (E_c , an index of myocardial contractility) and its diameter intercept (D_0) did not change after the intravenous infusion of ISDN (1, 5, 10, or 50 $\mu\text{g/kg/min}$). This suggests that ISDN infusion does not affect myocardial contractility in the normal in situ canine left ventricle.

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