原 著

The Effects of Dopamine and Nitroglycerin on the Size of Myocardial Ischemic Area in Dogs under Isoflurane Anesthesia

—A Thermographic Study—

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Abstract

A computerized experimental system is described that can visually display and quantify the size of the inchemic area of a beating heart using thermography. The ischemic area defined by this system is termed Thermographically Determined Myocardial Ischemic Area (TDMIA). This system includes monitoring and filing of heart rate, arterial pressure, cardiac output, end-tidal CO_2, anesthetic gas concentrations and temperatures. We have used the system to evaluate the effects of nitroglycerin and dopamine on cardiac function and coronary blood flow during ischemia. Nitroglycerin alone (0.5 μg/kg/min and 1 μg/kg/min) had no effect on TDMIA compared to control dogs. Nitroglycerin at 1 μg/kg/min with dopamine at 7.5 μg/kg/min significantly decreased TDMIA (vs. Baseline; P=0.002, vs. Control Group; p=0.046). Dopamine alone 7.5 μg/kg/min had the similar effect on TDMIA (vs. Baseline; p=0.0016, vs. Control Group; p=0.039). We speculated that dopamine increased the coronary flow of the ischemic area in this experimental model. We conclude that dopamine may have beneficial effects on myocardial ischemic area in the early phase of acute myocardial infarction in the canine model.

Key words : Heart : myocardial ischemia ; coronary blood flow, Pharmacology : nitroglycerin ; dopamine, Thermography

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Introduction

Nitroglycerin and dopamine are frequently used to improve cardiac function after acute myocardial infarction. Nitroglycerin is reported to increase coronary blood flow[1,2], decrease left ventricular filling pressure[3], lower calculated coronary collateral resistance[4], and lower systemic vascular resistance[1~5]. On the other hand, nitroglycerin may cause paradoxical deterioration of left ventricular (LV) function and either the new appearance or worsening of LV asynergy[6]. It is well documented that dopamine has a positive inotropic effect and increases overall cardiac performance. Dopamine is also reported to increase coronary blood flow and myocardial oxygen demand[7,8]. On the other hand, dopamine is reported to have the strong contractual effect on coronary arteries[9].

In order to clarify the effects of both nitroglycerin and dopamine on coronary flow during acute myocardial infarction, we developed a method for direct observation of the coronary blood flow and distribution in beating hearts. We utilized a computerized thermographic imaging system which

enables us to define ischemic areas as cold spots on beating hearts (Fig.1). The system is based upon a very high performance thermographic camera capable of recording 30 thermographic images per second, with a thermal resolution of 0.01℃. This level of temporal and thermal resolution produces a very clear visual thermographic video image of the beating heart. Additionally, the system produces a time-averaged thermogram from 256 frames that appears as a single image consisting of systolic and diastolic phases. An area of myocardial ischemia appears as cold spot on the thermogram that can be readily identified, and that we have defined as the Thermographically Determined Myocardial Ischemic Area (TDMIA). In 1971 Senyk et al. reported cardiothermography as a new method for detecting ischemic areas[10]. After this report some investigators suggested that thermographic imaging of ischemic hearts could reliably identify ischemic areas[9]. However, they could not observe ischemic areas in real time and continuously, because of the primitive nature of their thermographic cameras. This study is a reevaluation of the efficacy of thermography for detection of ischemic areas in a canine model using the high performance thermographic system. Additionally we have used the system to examine the effect of nitroglycerin and dopamine on LV function and coronary blood flow during ischemia.

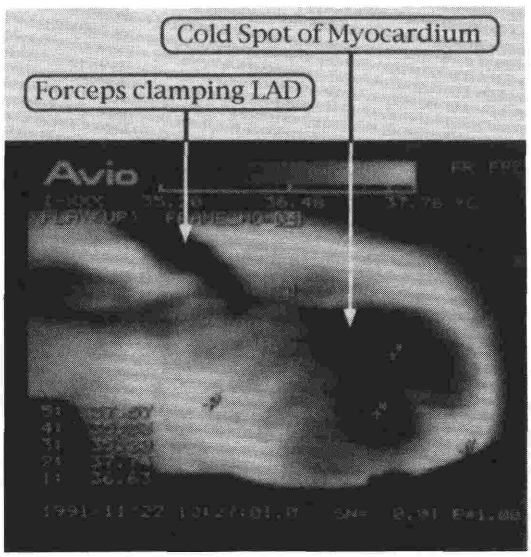

Fig. 1 A typical thermogram of the ischemic change induced by LAD occlusion. Black represents colder temperature. White arrows show clamping forceps and the cold spot.
LAD : left anterior descending coronary artery

Materials and Methods

The study protocol was approved by the Hokkaido University School of Medicine Animal Care and Use Committee. Twenty-eight mongrel dogs of either sex weighing 8 to 15 kg were equally divided into four groups.

Dogs were anesthetized wiht thiamylal 25 mg/kg IV ; vecuronium was used for muscle relaxation. After orotracheal intubation the dogs were mechanically ventilated (Servo 900-C, Siemens Sweden) with an inspired gas mixture of oxygen and nitrogen (1 : 1) and isoflurane 1.2 %, to maintain an end-tidal partial pressure of CO_2 between 35 to 40 mmHg. The right femoral vein and artery were catheterized for drug administration and arterial pressure measurement, respectively. Lactate Ringer's solution was administered at a rate of 10 mℓ /kg/hr using an infusion pump (STC- 503 Terumo, Tokyo, Japan) intravenously during the whole experiment. A left thoracotomy was performed at the fourth intercostal space and the heart suspended in a pericardial cradle. Then the left anterior descending coronary artery (LAD) was dissected from the surrounding tissue. An electromagnetic flow meter probe was placed around the ascending aorta to measure cardiac output (minus coronary flow) (MFV-3200, Nihon-Kohden, Tokyo, Japan). Arterial pressure was measured using a calibrated transducer (Uniflow Baxter, Deerfield, Illinois, USA). ECG and heart rate, esophageal and room temperatures (Bio View 2F37A, Nihondenki-Sanei, Tokyo Japan), and end-tidal CO_2 and isoflurane concentrations (5250 RGM Ohmeda, Louisville Connecticut, USA) were continuously monitored. A high performance thermographic camera (TVS-2000ME, Avionics, Tokyo, Japan) was used to measure the surface temperatures of the beating heart for each experiment. All of these data were collected and filed to an engineering work station (HP340C, Hewlett-

Packard, Waltham, Massachusetts, USA) (Fig.2). Because the surface temperature of the heart is a summation of the combined influences of the blood temperature, coronary blood flow, myocardial metabolism, and the ambient environmental temperature, the surface temperature (Ts) can be described by the following equation:

$$Ts = k \times Tab \times CBF + Tm + Te$$

Where each factor is defined as follows :

k ; constant number, CBF; coronary blood flow,

Tab ; temperature of arterial blood

Tm ; temperature made by myocardial metabolism

Te ; temperature affected by environment

During the experiments the ambient temperature was held constant and a constant anesthetic level was maintained to avoid myocardial metabolic change with resultant metabolism mediated myocardial temperature modulation. Given these conditions, the major remaining factors affecting the myocardial surface temperature are Tab and CBF. For this reason arterial blood temperature was continuously measured using a 5 Fr thermodilution catheter (Baxter, Deerfield Il. USA) with the thermister positioned in the thoracic aorta via the femoral artery. Blood temperature was used to correct the thermogram of the heart by adding an observed change in blood temperature to the thermographically measured myocardial surface temperature (Ts). Thus the remaining primary determinant fo Ts is coronary blood flow (CBF).

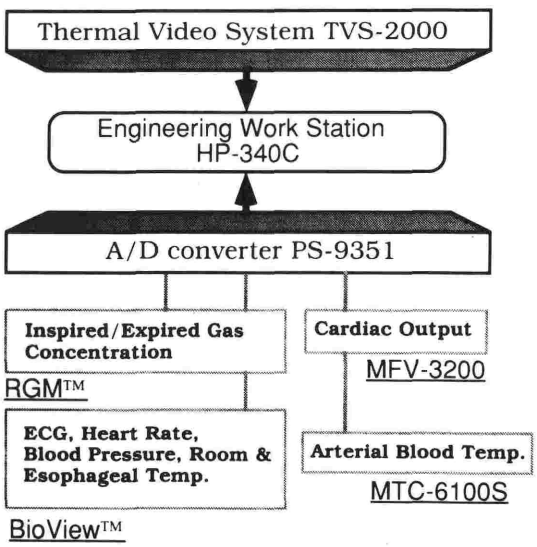

Fig. 2 A block diagram of the TDMIA analyzing system.
EWS : engineering work station

After this preparation and hemodynamic stabilization, a small clamp was used to completely occlude the LAD four separate times for 5 minutes each time. All LAD occlusions were separated by at least 20 min resting time. One group served as control (Group A, n=7), the next group received nitroglycerin (Nihon-kayaku, Tokyo, Japan) infusion alone (Group B, n=7) and the other group received nitroglycerin wiht dopamine (Kyowahakko, Tokyo, Japan) infusion (Group C, n=7) and the last group received dopamine infusion alone (Group D, n=7) during LAD occlusion. Each drug infusion was started 10 min before LAD clamping and stopped at the end of each LAD occlusion. The first occlusion was only for the set-up of the thermographic system, so that the thermographic camera could cover the ischemic area appropriately. The second occlusion was for the baseline measurement and served as control (unterated). The third and fourht occlusions were for durg administration. The third was for dose 1 ; nitroglycerin 0.5 μg/kg/min (0.5 mg/mℓ solution) and/or dopamine 5 μg/kg/min (2 mg/mℓ solution) (Groups B,C,D) and the fourth was for dose 2 ; nitroglycerin 1 μg/kg/min and/or dopamine 7.5 μg/kg/min infusion (Groups B,C,D). Syringe pumps (STC-521 Terumo, Tokyo, Japan) were used for accurate and constant infusions of test drugs (Fig. 3).

We defined the TDMIA as the total area in which individual pixels show temperatures during LAD occlusion of at least 0.5, 0.75, or 1.0 ℃ less than those before the LAD clamping. And these areas were named Hi-TDMIA, TDMIA, and Lo-TDMIA, respectively. The Hi-TDMIA is the total area in which Ts during LAD occlusion decreased more than 0.5 ℃ compared with before LAD clamping; TDMIA is the area in which temperature correspondingly decreased more than 0.75 ℃ ; and Lo-TDMIA is the area in which temperature decreased

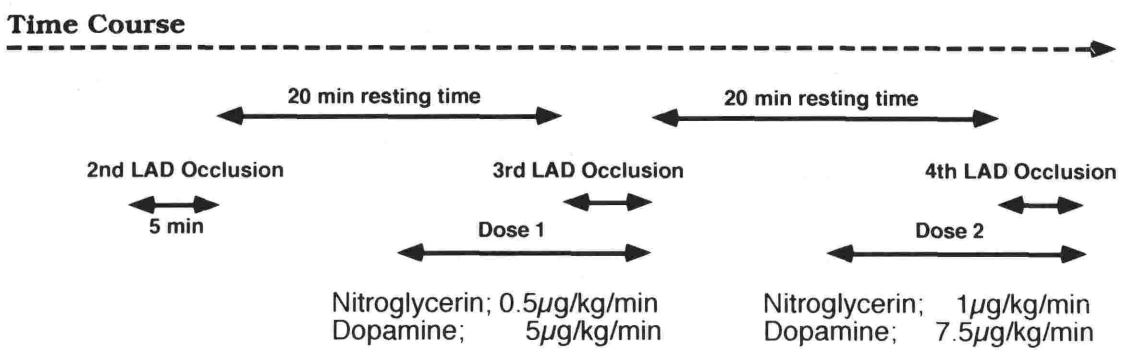

Fig. 3 The time course of the experiment

more than 1 ℃ during LAD occlusion. Because neither the angle of the thermographic camera relative to the myocardium, nor the distance between the camera and heart was controlled, the area measurements are relative rather than absolute. The TDMIAs observed during the second LAD occlusion served as the baseline value (100 %) and the TDMIAs observed with the third and fourth LAD occlusion were recorded as per cent changes.

The engineering work station collected the percent changes of the TDMIAs, heart rates, arterial blood pressure, cardiac output, end-tidal CO_2, anesthetic concentrations, room, esophageal, and arterial blood temperatures every 12 sec (5 data points/min for each variable). Each thermogram contained data from 256 frames. The TDMIAs and hemodynamic variables obtained over the last four min of LAD occlusion were time averaged to produce a single averaged data point for each occlusion period. Thus, each TDMIA is derived from data from 5120 (256 × 5 × 4) video frames of thermographic data and the corresponding hemodynamic data is the average of 20 (5 × 4) individual data points (Fig.4).

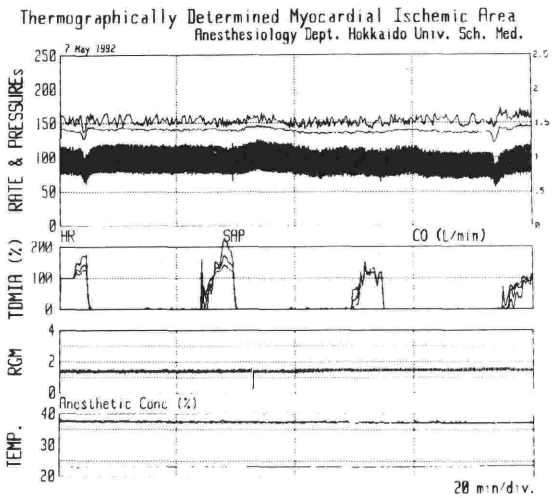

Fig. 4 A computer display of TDMIA analyzing system. A typical result of the experiment. In the top window, there are trends of heart rates, blood pressures, and cardiac output. In the next window, there is % change of TDMIA. In this experiment, the ischemic areas at the second LAD occlusion was defined 100% TDMIA.

In the next window, anesthetic gas concentrations were displayed. In the bottom window, esophageal, room, and arterial blood temperatures were displayed.

Data are presented as mean ± SEM. Statistical analysis was performed using the StatView Ⅳ statistical analysis program (Abacus Concepts Inc., Berkeley, CA., USA.). In each group, data of the third and fourth LAD occlusions were compared to that of the second occlusion, using analysis of variance (one way ANOVA) with *post hoc* analysis by Fisher's test. Groups were compared to each other using analysis of variance (ANOVA factorial) with *post hoc* analysis by Fisher's test. Differences were considered to be statistically significant if the P value was less than 0.05.

Results

There was a hyperemia period just after declamping the LAD each time, then Ts returned the level before LAD occlusion. Because of the correction by arterial blood temperature, even if the body temperature of the dog decreased slightly, TDMIAs before the third and fourth LAD occlusion were always 0 % (fig 4.).

In Group A (untreated), the TDMIA changed to 106 ± 15 % with the 3rd occlusion and 89 ± 9 % with the 4th occlusion. In Group B (nitroglycerin alone) TDMIA was 92 ± 13 % of the control value with 0.5 μg/kg/min (3rd occlusion) and 104 ± 12 % of control with 1.0 μg/kg/min (4th occlusion). In Group C (nitroglycerin plus dopamine) TDMIA was 91 ± 15 % of control with 0.5 μg/kg/min of nitroglycerin plus 5.0 μg/kg/min of dopamine (3rd occlusion) and 55 ± 14 % of control with 1.0 μg/kg/min of nitroglycerin plus 7.5 μg/kg/min of dopamine (4th occlusion). Wiht dopamine alone (Group D) TDMIA was 87 ± 6 % of control at 5.0 μg/kg/min (3rd occlusion) and 53 ± 11 % of control at 7.5 μg/kg/min (4th occlusion). In Groups C and D, the TDMIAs of dose 2 were significantly different from those of dose 1 and the baseline measurement of the second occlusion (Fig. 5). TDMIAs of dose 2 in Groups C and D were significantly smaller than those of Groups A and B (Fig. 5). In Groups C and D, the Hi-TDMIAs of dose 2 were significantly different from those of dose 1 and the baseline (Fig. 6). Hi-TDMIA of dose 2 in Group C was significantly smaller than those of Groups A and B and also Hi-TDMIA of dose 2 in Group D was significantly smaller than that of Group A (Fig. 6). In Group A, the Lo-TDMIA of the third occlusion was significantly different from that of the second occlusion (Fig. 7). In Group C, the Lo-TDMIA of dose 2 was significantly different from that of the baseline (Fig. 7). Lo-TDMIAs of dose 1

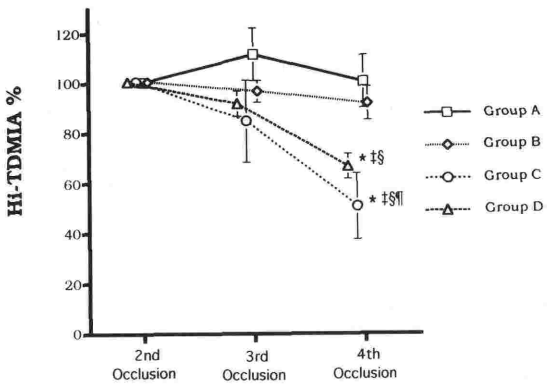

Fig. 6 Hi-TDMIA changes in Groups A, B, C, and D.
*p <0.05 Paired to Baseline
‡p <0.05 Paired to Dose 1
§p <0.05 Paired to Control Group (A)
¶p <0.05 Paired to Nitroglycerin Group (B)

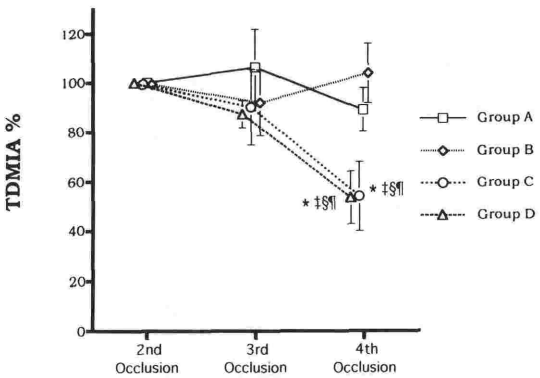

Fig. 5 TDMIA changes in Groups A, B, C, and D.
*p <0.05 Paired to Baseline
‡p <0.05 Paired to Dose 1
§p <0.05 Paired to Control Group (A)
¶p <0.05 Paired to Nitroglycerin Group (B)

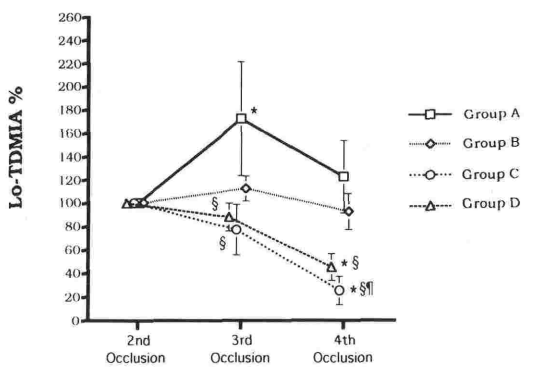

Fig. 7 Lo-TDMIA changes in Groups A, B, C, and D.
*p <0.05 Paired to Baseline
‡p <0.05 Paired to Dose 1
§p <0.05 Paired to Control Group (A)
¶p <0.05 Paired to Nitroglycerin Group (B)

in Groups C and D were significantly smaller than that of Group A, Lo-TDMIA of dose 2 in Group C was significantly smaller than those of Groups A and B and Lo-TDMIA of dose 2 in Group D was significantly smaller than that of Group A (Fig. 7).

Systolic and diastolic blood pressures, cardiac output, and heart rates are shown in the table. There were no significant differences in systolic and diastolic blood pressures and heart rates of baseline measurement in each group. Although the baseline cardiac output of Group A was significantly larger than that of GroupB (1.65 ± 0.13 vs. 1.20 ± 0.14 ℓ/min), there was no significant difference among other groups (Group C ; 1.27 ± 0.16, Group D ; 1.30 ± 0.14 ℓ/min).

Discussion

In the early phase of an acute myocardial infarction (AMI), the size of ischemic areas may change depending on the collateral circulation. Simultaneous analysis of changes in ischemic areas and hemodynamic variables by the thermographic system was applied to an experimental AMI model. The surface temperature of the heart represents mainly a combination of the blood temperature and the coronary blood flow, and with constant blood temperature the surface temperature represents the blood flow. This thermographic system can thus observe directly the size of an ischemic area in real time.

The ischemic area used to be measured pathologically and biochemically after autopsy, or by coronary angiography or by nuclear medical technics in human studies. These methods could not measure changes of ischemic areas continuously in real time. Additionally, thermographic imaging does not require direct contact with the heart so that the heart itself is not damaged due to any electrodes.

Tsuchida et al. reported the effects of thoracic epidural anesthesia on myocardial pH and metabolism during ischemia in dogs using the similar experimental settings. They applied 5 min LAD occlusions four times on each dog and confirmed the reproducibility of ischemic changes due to the coronary occlusions[11].

We chose three temperatures (0.5, 0.75. 1.0 ℃) for detecting ischemic changes as cold spots according to the results of the preliminary experiments. Hi-TDMIA surrounded the TDMIA and meant the border area of the ischemic part. Although, in the present study, changes of Hi-TDMIA was similar to TDMIA, there may exist some possibilities to detect the change of coronary flow distributions due to collateral flow. Lo-TDMIA was at the center part of the TDMIA. This area was relatively small so that percent changes were emphasized more than TDMIA and Hi-TDMIA. This fact might be one of the possible reasons why there was the significant difference in Lo-TDMIAs between the second and third LAD occlusions of Group A. Probably because of the same reason, there were significant differences between Lo-TDMIAs of Group A vs. C and A vs. D at dose 1 (Fig. 7).

Jugdutt et al[1]. demonstrated that intravenous nitroglycerin reduced infarct size in an unanesthetized canine model of AMI by the mechanism of increasing inter coronary collateral flow. Although nitroglycerin was thought to dilate the coronary collateral arteries[1,2], in the present study, it did not decrease the TDMIA significantly (Fig. 5). A possible reason for this fact is that the effect of nitroglycerin on arterial pressure and cardiac output may overcome the dilating effect on the coronary artery under isoflurane anesthesia. The other possible reason is that nitroglycerin dilates large coronary arteries more than small coronary arteries compared to adenosine as shown by Fam et al[12]. Then we might not be able to detect the increased global coronary flow because the TDMIA method was the detector of colder temperature but could not detect warmer temperature in intact area due to increased blood flow unless the TDMIA decreased.

Our results indicated that dopamine with or without nitroglycerin decreased the TDMIA significantly. The combination of dopamine and nitroglycerin produced a significant increase of diastolic pressure, and the coronary perfusion pressure (CPP) might be significantly higher because CPP

could be approxmately calculated by diastolic pressure and right atrial pressure. The hemodynamic effects of dopamine with or without nitroglycerin may increase coronary blood flow even in the ischemic area through collateral vessels. Although dopamine increased the coronary blood flow in this model of AMI, this may not be beneficial in terms of myocardial survival if the coronary blood flow increase is due to increased myocardial oxygen demands[8]. It is possible that nitroglycerin may reduce the disadvantageous effects of dopamine due to attenuating hemodynamic effects on cardiac output and myocardial oxygen demands[3,4]. Indeed, in the present study, dopamine produced significant increases of cardiac output and nitroglycerin attenuated this effect of dopamine (Table). Also it is important that heart rate was not changed significantly with drug administration in any group because an excessive increase of heart rate is responsible for an increase of myocardial oxygen demands.

Dopamine is often combined with nitroglycerin in early phase of AMI, because nitroglycerin alone produces further decreases in cardiac output and blood pressure as shown in the table. In this study, the benefit of dopamine and nitroglycerin infusions to myocardial inchemic areas was reevaluated in the canine model.

The principle finding of this study was that this thermographic system is extremely useful to detect the coronary blood flow under an experimental AMI model and we conclude that dopamine combined with nitroglycerin may have beneficial effects on myocardial ischemic areas in the early phase of AMI. The prophylactic use of dopamine with or without nitroglycerin may reduce the ischemic area if heart rates and myocardial oxygen demands are well maintained within a physiological range.

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Table. Hemodynamic Variables

		Baseline (2nd Occlusion)	Dose 1 (3rd Occlusion)	Dose 2 (4th Occlusion)
Systolic BP (mmHg)	(A) Control	127±7.1	128±7.7	126±8.1
	(B) Nitroglycerin	128±4.1	119±3.8	117±3.4
	(C) NTG+Dopamine	134±11	143±10.9	159±10 ¶
	(D) Dopamine	126±8.5	130±10	161±20.7*‡ ¶
Diastolic BP (mmHg)	(A) Control	86±5.8	87±6.5	86±7.1
	(B) Nitroglycerin	88±3.7	84±3.5	85±3.3
	(C) NTG+Dopamine	89±6.2	96±5.9	109±6.9*§ ¶
	(D) Dopamine	85±6.8	85±8	99±11.7
Heart Rate (bpm)	(A) Control	143±6.7	144±6.8	143±6.6
	(B) Nitroglycerin	155±8.8	148±8.5	149±8.1
	(C) NTG+Dopamine	145±8.6	151±9.5	154±8.8
	(D) Dopamine	151±4.7	152±4.5	160±7.1
Cardiac Output (ℓ/min)	(A) Control	1.52±0.17	1.51±0.18	1.65±0.26
	(B) Nitroglycerin	1.20±0.14	1.12±0.13	1.09±0.13
	(C) NTG+Dopamine	1.27±0.16	1.32±0.14 ¶	1.35±0.10
	(D) Dopamine	1.30±0.14	1.44±0.15§ ¶	1.68±0.15*§ ¶i

mean ± SEM
NTG = nitroglycerin

* $p < 0.05$ Paired to Baseline
‡ $p < 0.05$ Paired to Dose 1
§ $p < 0.05$ Paired to Control group (A)
¶ $p < 0.05$ Paired to Nitroglycerin group (B)
i $p < 0.05$ Paired to NTG+Dopamine group (C)

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