Effect of Combined Dopamine and Bunazosin on the Ischemic Heart after Occlusion of the Coronary Artery

Tomoe KATOH, Fumiki MORI, Masaki MIYAMOTO and Kensuke ESATO

ABSTRACT: In order to investigate whether dopamine combined with bunazosin improves cardiac function, the global and regional cardiac function and regional blood flow of 7 anesthetized dogs were analyzed before and after occlusion of the left anterior descending coronary artery (LAD), then after 10 μg/kg/min dopamine infusion following the LAD occlusion, and again after a bolus infusion of bunazosin 250 μg/kg. Dopamine with bunazosin reduced left atrial pressure from 4.9 $\pm$ 0.9 to 3.1 $\pm$ 0.5 mmHg ($p<0.05$) and improved cardiac output from 1.22 $\pm$ 0.15 to 1.50 $\pm$ 0.14 L/min ($p<0.05$), maximum positive left ventricular dp/dt from 1721 $\pm$ 202 to 3600 $\pm$ 663 mmHg/sec ($p<0.05$) and the time constant from 45.2 $\pm$ 5.0 to 27.5 $\pm$ 4.6 msec ($p<0.01$). Bunazosin added to the dopamine reduced the elevated left ventricular peak systolic pressure caused by dopamine from 130 $\pm$ 7 to 113 $\pm$ 8 mmHg ($p<0.01$). With regard to the regional wall motion, the impaired LAD-ΔL (the segment systolic shortening) and LAD-Elmax (the slope of peak systolic pressure—endsystolic length relation) following the LAD occlusion improved from 0.5 $\pm$ 2.5 per cent to 5.9 $\pm$ 2.6 per cent ($p<0.01$) and from 50 $\pm$ 9 to 82 $\pm$ 14 mmHg/mm ($p<0.01$) after the infusion of dopamine with bunazosin. Dopamine greatly increased the Rate Pressure Product (RPP) from 12610 $\pm$ 1120 after LAD occlusion to 16950 $\pm$ 1420, whereas dopamine in combination with bunazosin did not increase the RPP due to a drop of LV-PSP with little change in regional myocardial blood flow. It was concluded that combining dopamine with bunazosin was useful for improving both the global and regional cardiac functions of the ischemic heart.

KEY WORDS: ischemic heart, dopamine, bunazosin, regional myocardial wall motion, regional myocardial blood flow

INTRODUCTION

Dopamine is widely used in the treatment of heart failure as an inotropic agent. However, it is likely to augment afterload and also induces arrhythmia with dose dependency,[1,2] these side effects being potentially deleterious to the ischemic heart. Bunazosin is a vasodilator whose action results from an α_1 blocking effect,[3] which reduces preload and afterload against heart failure,[4] dilates the coronary arteries,[5] and inhibits arrhythmia after coronary reperfusion.[6] We therefore were of the opinion that dopamine in combination with bunazosin might possess advantages for the management of cardiac

The First Department of Surgery, Yamaguchi University School of Medicine, Ube, Yamaguchi, Japan

Reprint requests to: Tomoe Katoh, MD, The First Department of Surgery, Yamaguchi University School of Medicine, Ube, Yamaguchi 755, Japan

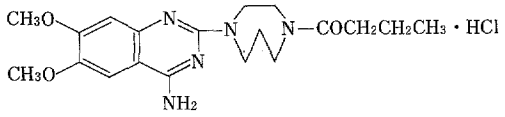

Fig. 1. Structure of bunazosin hydrochloride.

failure caused by ischemia. The aim of this study was to evaluate the dffectiveness of such a combined therapy for ischemic heart failure following acute coronary artery occlusion in a canine model.

Matrials and Methods

Seven mongrel dogs weighing between 6.0 and 15.5 kg were anesthetized with intravenous sodium pentobarbital 25 mg/kg and maintained on a respirator. After a thoracotomy had been performed through an incision in the left fifth intercostal space, the heart was exposed and suspended by a pericardial cradle. Swan-Ganz catheter (Edwards, USA) was then inserted into the right pulmonary artery from the left internal jugular vein, and a Muller type micromanometer-tipped catheter inserted into the left ventricular cavity through the cardiac apex. To assess regional myocardial wall motion, a pair of ultrasonic crystals, 1–2 mm in diameter was implanted in the subend-cardium in an ischemic area where the left anterior descending coronary artery (LAD) was occluded and in a normal area perfused by the left circumflex coronary artery (LCX). Two wire-type platinum probes, 100 μm in diameter, were positioned in the middle layer of myocardium for measurement of regional myocardial blood flow by the hydrogen gas clearance method,[7] while one probe was positioned in an area of normal myocardium (LCX-flow), and the other in the ischemic area (LAD-flow) (Fig. 2).

The parameters of hemodynamics consisted of: heart rate (HR), cardiac output (CO), left ventricular peak systolic pressure (LV-PSP), maximum positive LVdp/dt (positive dp/dt), maximum negative LVdp/dt

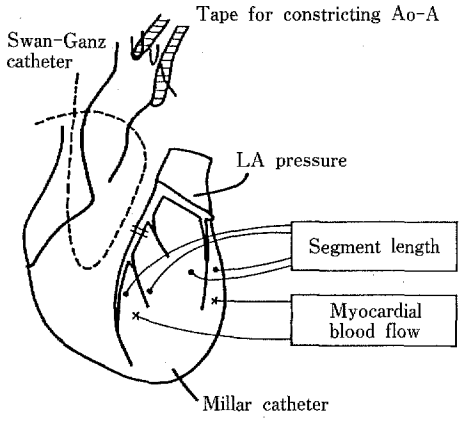

Fig. 2. Experimental schema.
Ao-A, aortic arch; LA, left atrium; LAD, left anterior descending coronary artery

(negative dp/dt) and the time constant of isovolumic pressure fall (TC) calculated by Weiss's method.[8] Variables studied with regional wall motion on the ischemic and normal areas were end-diastolic segment length (LAD-EDL, LCX-EDL), which was normalized by dividing the observed length by the control end-diastolic segment length before the occlusion of LAD and multiplying it by ten, and segment systolic shortening (LAD-ΔL, LCX-ΔL). The regional myocardial contractility was obtained by the slope of peak systolic pressure—endsystolic length relation (Elmax), derived from a linear regression analysis on 6–10 beats during the elevation of LV-PSP by means of constricting the aortic arch gradually with teflon tape. Pressure and regional wall motion were recorded with a Polygraph system 360 (Nippon Denki Sanei, Japan) (Fig. 3). Global cardiac function, regional wall motion and contractility, and regional myocardial blood flow were measured in the stable state of hemodynamics before and after LAD occlusion, after dopamine infusion (10 μg/kg/min), and then again after the infusion of bunazosin (250 μg/kg). With respect to the dose of dopamine, we selected a 10 μg/kg/min infusion of dopamine which clearly

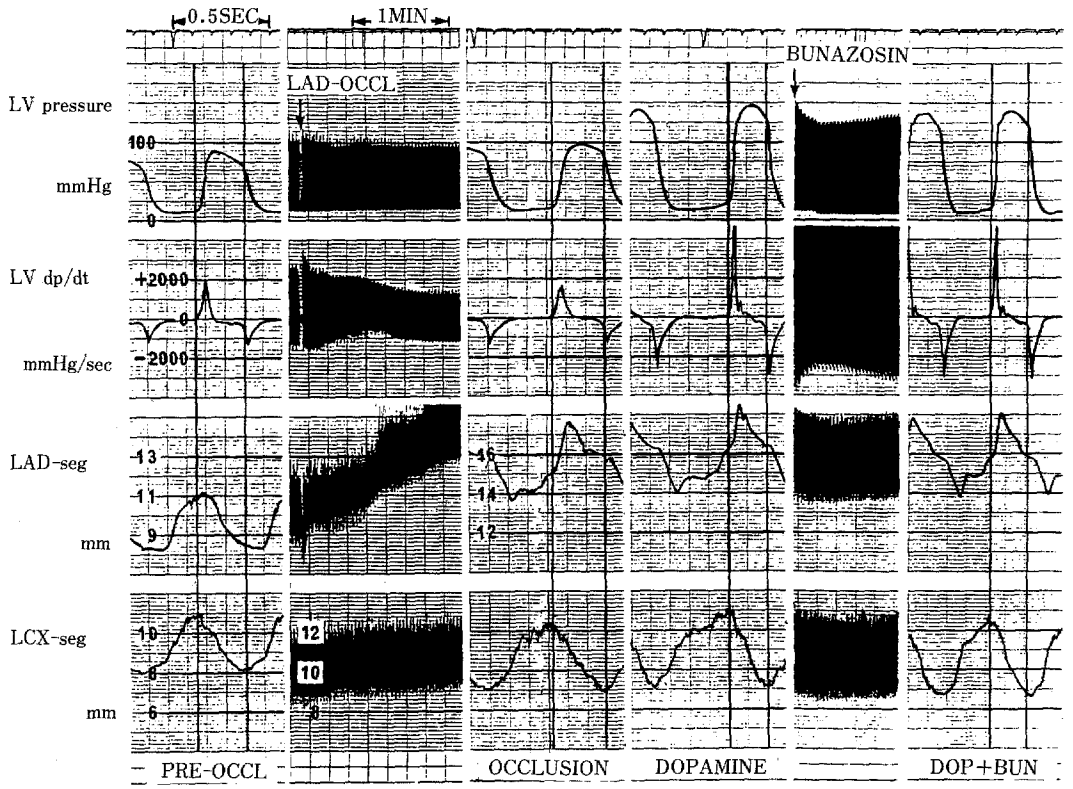

Fig. 3. Changes in LV pressure, LVdp/dt and regional segment length: (Example case). The LAD-segmental wall, which moved paradoxically after LAD occlusion, improved contraction by both dopamine and dopamine with bunazosin. The LCX-segmental wall, which compensively moved hyperkinetic after LAD occlusion, tended to increase contraction by both dopamine and dopamine with bunazosin. LV, left ventricle; LAD-seg, segmental wall motion of ischemic area; LCX-seg, segmental wall motion of the normal segment; PRE-OCCL, before LAD occlusion; OCCLUSION, LAD occlusion; DOP, dopamine infusion; DOP + BUN, infusion of dopamine with bunazosin

possessed an α-stimulating effect and which could have an adverse effect on the ischemic myocardium. We thought this dose of dopamine useful to investigate the myocardial protecting effect and the α_1-blocking effect of bunazosin. The administered dosage of bunazosin, which was determined to obtain a 10 to 20 per cent reduction in LVP-PSP by a preliminary study, was 250 μg/kg.

Analysis of these data was performed using the t-test for paired data. Data were considered significant when P values were less than 0.05 and results are expressed as the mean $\pm$ standard error (SE).

Results

HR, CO and positive dp/dt

The HR decreased from 134 $\pm$ 10 beats/min before LAD occlusion to 121 $\pm$ 11 beats/min following LAD occlusion ($p<0.05$). It then increased to 131 $\pm$ 12 beats/min after the dopamine infusion ($p<0.01$). However, dopamine in combination with bunazosin, did not result in a significant increase in the heart rate. The CO decreased from 1.34 $\pm$ 0.19 L/min before LAD occlusion to 1.22 $\pm$ 0.15 L/min afterward ($p<0.05$) and increased

Table 1. Global Cardiac Function

	Pre-Occl	Occlusion	Dopamine	DOP+BUN
HR	134±10	121±11	131±12	147±8
LAP	3.8±0.4	4.9±0.9	3.4±0.3	3.1±0.5
LV-PSP	113±9	105±8	130±7	113±8
+dp/dt	2300±266	1721±202	3250±453	3600±663
−dp/dt	1993±273	1600±220	2193±271	1593±310
CO	1.34±0.19	1.22±0.15	1.44±0.17	1.58±0.14
CT	30.6±3.0	45.2±5.0	30.0±4.4	27.5±4.6

PREOCCL: before LAD occlusion, DOP+BUN, dopamine with bunazosin, HR, heart rate (beats/min); LAP, left atrial pressure (mmHg); LV-PSP, left ventricular peak systolic pressure (mmHg); +dp/dt, maximum positive dp/dt (mmHg/sec); −dp/dt, maximum negative dp/dt (mmHg/sec); CO, cardiac output (l/min); TC, time constant (msec); *, $p<0.05$; **, $p<0.01$

from 1.22 ± 0.15 to 1.44 ± 0.17 L/min during the dopamine infusion ($p<0.05$) and tended to further increase to 1.58 ± 0.14 L/min after the administration of dopamine with bunazosin. The value of positive dp/dt decreased from 2300 ± 266 mmHg/sec before LAD occlusion to 1721 ± 202 mmHg/sec following LAD occlusion ($p<0.01$), though this value increased to 3250 ± 453 mmHg/sec after the dopamine infusion ($p<0.05$). Dopamine with bunazosin tended to increase the positive dp/dt more than dopamine alone.

Preload and afterload

The LAP which tended to rise after LAD occlusion fell from 4.9 ± 0.9 to 3.1 ± 0.5 mmHg after the administration of dopamine with bunazosin ($p<0.05$). Although the LV-PSP, which did not change following LAD occlusion, rose from 105 ± 8 to 130 ± 7 mmHg after the dopamine infusion ($p<0.01$), it fell to 113 ± 8 mmHg with a statistically significant difference ($p<0.01$) after dopamine with bunazosin.

Left ventricular relaxation

The negative LVdp/dt fell to 1600 ± 220 mmHg/sec following LAD occlusion ($p<0.05$), but increased to 2193 ± 271 mmHg/sec after the dopamine infusion ($p<0.05$). Bunazosin did not affect the negative dp/dt significantly. A significant increase in TC occurred after LAD occlusion. Dopamine shortened the TC from 45.2 ± 5.0 to 30.0 ± 4.4 msec ($p<0.01$), while dopamine with bunazosin tended to further shorten it from 30.0 ± 4.4 to 27.5 ± 4.6 msec.

Regional myocardial wall motion

The LAD-EDL (ischemic area), which increased from 10.0 mm before LAD occlusion to 11.4 ± 0.4 mm ($p<0.01$) after LAD occlusion, was insignificantly changed after the infusion of either dopamine or dopamine with bunazosin, The LCX-EDL (normal area), which increased slightly from 10.0 mm before LAD occlusion to 10.6 ± 0.1 mm after LAD occlusion ($p<0.01$), showed minimal change after the dopamine infusion but decreased to 10.2 ± 0.2 mm after dopamine with bunazosin.

The LAD-ΔL decreased from 15.9 ± 2.2 per cent before LAD occlusion to 0.5 ± 2.5 per cent after LAD occlusion ($p<0.01$). Dopamine increased it from 0.5 ± 2.5 to 5.1 ± 2.1 per cent ($p<0.01$), while dopamine with bunazosin also increased it from 0.5 ± 2.5 to 5.9 ± 2.6 per cent ($p<0.01$). The LCX-ΔL tended to increase from 12.9 ± 2.3 per cent

Table 2. Regional Myocardial Wall Motion and Regional Myocardial Blood Flow

	Pre-Occl	Occlusion	Dopamine	DOP+BUN
LAD-EDL	10.0	11.4±0.4	11.1±0.5	11.0±0.6
LCX-EDL	10.0	10.6±0.1	10.4±0.2	10.2±0.2
LAD-ΔL	15.9±2.2	0.5±2.5	5.1±2.1	5.9±2.6
LCX-ΔL	12.9±2.3	14.2±2.3	15.3±2.6	14.8±2.9
LAD-El max	125±22	50±9	65±13	82±14
LCX-El max	152±22	104±16	216±36	240±36
LAD-flow	90.8±6.6	18.3±7.1	24.4±6.7	22.3±6.9
LCX-flow	80.7±10.5	72.6±12.4	100±13.0	89.4±12.6

PRE-OCCL: before LAD occlusion, DOP+BUN, dopamine with bunazosin, LAD-EDL, end diastolic length of ischemic segment (mm); LCX-EDL, end-diastolic normal segment (mm); LAD-ΔL, segmental systolic shortening of ischemic area (%); LCX-ΔL, segmental systolic shortening of normal area (%); LAD-El max, segmental elastance of ischemic area (mmHg/mm); LCX-El max, segmental elastance of normal area (mmHg/mm); LAD-flow, myocardial blood flow of ischemic area (ml/min/100 g); LCX-flow, myocardial blood flow of normal area (ml/min/100 g); *, $p<0.05$; **, $p<0.01$

before LAD occlusion to 14.2 ± 2.3 per cent after LAD occlusion, and to 15.3 ± 2.6 per cent after the dopamine infusion, then to 14.8 ± 2.9 per cent after the administration of dopamine with bunazosin.

Though the LAD-Elmax decreased from 125 ± 22 mmHg/mm before LAD occlusion to 50 ± 9 mmHg/mm after LAD occlusion, this level was not increased by the dopamine infusion. However, following the administration of dopamine with bunazosin, the LAD-Elmax increased from 50 ± 9 to 82 ± 14 ($p<0.05$).

The LCX-Elmax decreased insignificantly after LAD occlusion, then increased from 104 ± 16 to 216 ± 36 mmHg/mm after the dopamine infusion ($p<0.01$) and to 240 ± 36 mmHg/mm after the dopamine with bunazosin infusion ($p<0.01$).

Regional myocardial blood flow

The LAD-flow decreased from 90.8 ± 6.6 to 18.3 ± 7.1 ml/min/100 g after LAD occlusion ($p<0.01$), then increased to 24.4 ± 6.7 ml/min/100 g after the dopamine infusion ($p<0.05$). There was no statistically significant difference between these levels after the administration of dopamine or dopamine with bunazosin.

The LCX-flow increased from 72.6 ± 12.4 ml/min/100 g after LAD occlusion to 100 ± 13 ml/min/100 g after the dopamine infusion and dopamine with bunazosin did not significantly change the LCX-flow after the dopamine infusion.

Discussion

Although dopamine is employed extensively in the treatment of heart failure, it may induce arrhythmia and increase the α-stimulating effect when given at a high infusion rate (5–10 μg/kg/min).[1,2] It may also cause further damage to the myocardium in patients with coronary artery disease due to its myocardial stimulating effects.[9,10] Bunazosin, which belongs to the quinazolin derivatives, selectively inhibits the postsynaptic receptors (α_1-receptor) with little inhibition of the presynaptic receptors (α_2-receptor).[3] Consequently, bunazosin minimizes the release of norepinephrine stimulated by a negative feedback mechanism.[11] Vasodilator therapy

using phentholamine for an ischemic heart may induce tachycardia and worsen angina because phentholamine blocks not only the α_1-receptors but also the α_2-receptors resulting in release of norepinephrine, leading to positive chronotropic and inotropic effects.[11] We were of the opinion that vasodilator therapy using bunazosin might be especially useful because it rarely causes the release of norepinephrine. Bunazosin reduces the preload and afterload of heart failure, has a direct vasorelaxant effect, blocks α adrenoceptor activity in the coronary arteries,[5] and prevents arrhythmia during coronary reperfusion.[6] It could therefore be assumed that bunazosin might be beneficial to an ischemic heart because of the balanced vasodilator effects and the protection of ischemic myocardium after coronary occlusion, however bunazosin when used alone may reduce mean arterial pressure and result in worsening the ischemia of the ischemic heart. As with the combined nitroprusside-dopamine therapy of heart failure, the concomitant administration of dopamine and bunazosin might also be beneficial to the ischemic heart and compensate for each disadvantage in the isolated use of dopamine. Although combined nitroprusside-dopamine therapy sometimes is used for heart failure, there are reports that vasodilation by nitroprusside is without significant effects on the regional function of the infarcted zone,[12] and that after several days of nitroprusside administration a trade-off between the reduction in ventricular filling pressure and afterload might occur.[13] These phenomena have not been reported about bunazosin.

HR, CO and positive dp/dt

Although dopamine with bunazosin increased the HR compared to the HR after LAD occlusion, it did not significantly increase the HR more than dopamine alone. As an increase in HR may cause deterioration of the ischemic heart, caution must be paid.

CO, which helps monitor pump function, increased after the infusion of dopamine with bunazosin. This increase in CO was due to the increase in HR and the improvement of cardiac contractility because positive dp/dt, indicating the inotropic state of the myocardium, was increased by both dopamine and dopamine with bunazosin.

Preload and afterload

The administration of 10 μg/kg/min dopamine improved cardiac systolic function despite the increase in LV-PSP levels. The enhancement of afterload is disadvantagous to the ischemic heart due to increased cardiac external work and oxygen consumption. Vasodilator therapy for cardiac failure improves cardiac function by reducing the afterload and preload, and by reducing the myocardial oxygen consumption and decreasing myocardial wall tension. Nevertheless, therapy may worsen ischemia by reducing the coronary perfusion pressure, especially when the blood pressure is low. Dopamine with bunazosin reduced LV-PSP after the dopamine infusion without causing hypotension. Therefore, the moderate reduction in preload and afterload caused by dopamine with bunazosin is useful for treating ischemic heart failure.

Left ventricular relaxation

Both negative dp/dt and TC are indices of left ventricular relaxation.[8,14] The negative dp/dt is affected mainly by LV-PSP, while TC is independent of stroke volume, LV-PSP, fiber shortening velocity and end-systolic fiber length and minimally dependent on heart rate.[8,15] Moreover, TC rises with the ischemia of the heart.[16] The negative dp/dt tended to decrease after the infusion of dopamine with bunazosin, and this tendency might be affected by the decreased LV-PSP. The increased TC after LAD occlusion was shortened after both the dopamine infusion and the dopamine with bunazosin infusion. Therefore, it is possible that dopamine with bunazosin improves left ventricular relaxation.

Regional myocardial wall motion

LCX-EDL decreased after the infusion of dopamine with bunazosin, which suggests

that dopamine with bunazosin decreases preload and corresponds to the results that LAP also decreased after this therapy. LAD-ΔL, which decreased after LAD occlusion, increased following the administration of dopamine with bunazosin, showing that the contraction of the ischemic area might be improved by this therapy. Emax is independent of preload and afterload and reflects the global cardiac contractility.[17] Emax can be gained from peak systolic pressure as a substitute for end-systolic pressure,[18] and so we used the peak systolic pressure for calculating Elmax. Tomoike and coworkers[19] reported that the slope of the endsystolic pressure-length relation (Elmax) changed in a manner similar to that seen with the pressure-volume relation (Emax). Elmax might be an index of regional myocardial contractility, although this is controversial.[19,20] In this study, dopamine alone did not significantly change LAD-Elmax but greatly increased LCX-Elmax. Compared with dopamine alone, dopamine with bunazosin increased LAD-Elmax and also tended to increase LCX-Elmax. Therefore, dopamine with bunazosin might be useful mainly for improving the contractility of ischemic myocardium.

Myocardial blood flow and oxygen consumption

Although dopamine might directly cause ischemic myocardial contraction, we investigated its other effects that might affect myocardial contractility, such as regional myocardial blood flow and myocardial oxygen consumption. Dopamine slightly increased the blood flow of both the ischemic and normal myocardial areas, which is decreased after LAD occlusion, as Brooks[21] reported. This phenomenon suggests an increase in oxygen supply, however, myocardial oxygen demand presented by the Rate Pressure Product (RPP) greatly increased with the dopamine infusion. These results suggest that dopamine may worsen ischemia through an increase in myocardial oxygen consumption. Dopamine in combination with bunazosin did not result in a significant increase in myocardial blood flow of the ischemic area (LAD area) or normal area (LCX area), and did not increase RPP, compared with dopamine alone. A 50 per cent increase in HR results in a 50 per cent increase in myocardial oxygen consumption but in fact there is little change in myocardial oxygen consumption per beat.[22] The rise in LV-PSP brought and increase in pressure work, which resulted in a large increase in myocardial oxygen consumption.[23] We considered that the increase in LV-PSP may greatly affect the increase in myocardial oxygen consumption more than the increase in HR. Dopamine with bunazosin minimized the elevation in LV-PSP which had been obtained during the dopamine infusion. Therefore, it is probable that the reducing effects of RPP and LV-PSP by a combination of bunazosin reflect the decrease in myocardial oxygen consumption and improve the balance between myocardial oxygen supply and demand.

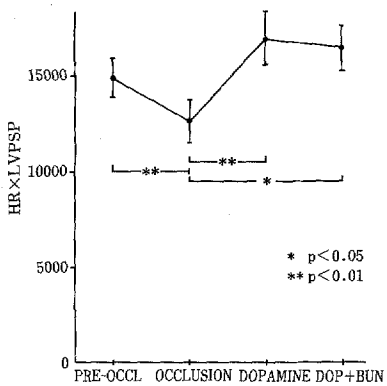

Fig. 4. Rate pressure product (RPP). HR, heart rate, LV-PSP, left ventricular systolic pressure

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