Different Effects of Propranolol, Phenylephrine, and Saline Volume Loading on Catecholamine-Induced Left Ventricular Outflow Tract Obstruction in Acute Coronary Syndrome

Ichiro OHBA,¹ MD, Yutaka OTSUJI,¹ MD, Kensaburo SHIKI,¹ MD, Shuichi HAMASAKI,¹ MD, Shinichi MINAGOE,¹ MD, and Chuwa TEI,¹ MD

SUMMARY

Hemodynamic deterioration due to left ventricular outflow tract (LVOT) obstruction can occur during catecholamine infusion in patients with acute coronary syndrome (ACS). The purpose of the present study was to compare the utility of propranolol, phenylephrine infusion, and rapid saline loading for reversal of dobutamine-induced LVOT obstruction in a canine model of ACS. ACS was induced via left anterior descending artery ligation in 21 open-chest anesthetized dogs, and LVOT obstruction, defined as an LVOT gradient > 30 mmHg, was induced by dobutamine infusion (20 to 40 $\mu\text{g/kg/min}$). Subsequently, the effects of propranolol infusion (0.7 to 1.0 $\mu\text{g/kg/min}$, $n = 8$), phenylephrine infusion (10 to 200 $\mu\text{g/kg/min}$, $n = 7$), and saline loading (200 to 400 mL/hr, $n = 6$) were assessed by serial hemodynamic measurements. All interventions produced significant and comparable improvements in the LVOT pressure gradient (propranolol: 60 ± 16 to 15 ± 12 ; phenylephrine: 68 ± 15 to 12 ± 10 ; saline loading: 58 ± 18 to 22 ± 10 mmHg; $P < 0.001$ for baseline versus postintervention; $P = \text{NS}$ for comparison between interventions). Phenylephrine produced the greatest elevation in aortic pressure (propranolol: $+15 \pm 13$; phenylephrine: $+51 \pm 36$; saline loading: $+15 \pm 15$ mmHg; $P < 0.05$), while saline loading produced the greatest increase in cardiac output (propranolol: $+0.05 \pm 0.12$; phenylephrine: $+0.28 \pm 0.37$; saline loading: $+0.73 \pm 0.48$ L/min; $P < 0.05$). Propranolol was the only intervention that produced a significant decrease in diastolic pulmonary artery pressure (16 ± 5 to 11 ± 3 mmHg, $P < 0.05$). Propranolol, phenylephrine infusion, and saline volume loading were similarly effective in reversing dobutamine-induced LVOT obstruction in this canine model of ACS. However, each intervention produced different hemodynamic effects with potentially different clinical indications. (Int Heart J 2006; 47: 287- 295)

Key words: Acute coronary syndrome, Mitral valve, Congestive heart failure

From the ¹ First Department of Internal Medicine, Kagoshima University School of Medicine, Kagoshima, Japan.

Address for correspondence: Yutaka Otsuji, MD, First Department of Internal Medicine, Kagoshima University School of Medicine, 8-35-1 Sakuragaoka, Kagoshima City, Kagoshima 890-8520, Japan.

Received for publication July 14, 2005.

Revised and accepted November 14, 2005.

LEFT ventricular outflow tract (LVOT) obstruction may occur in response to catecholamine infusion in patients with acute coronary syndrome (ACS),¹⁻⁵⁾ thereby resulting in serious hemodynamic deterioration. Previous reports have demonstrated that administration of a β -adrenoceptor blocker⁶⁾ or an α -adrenergic stimulator,⁷⁾ and avoidance of hypovolemia⁷⁾ can reverse LVOT obstruction in patients with hypertrophic obstructive cardiomyopathy. However, other studies have reported that LVOT obstruction was not relieved by discontinuation of catecholamine, administration of a β -adrenoceptor blocker, administration of an α -adrenergic antagonist, or saline volume infusion in patients with ACS.¹⁻⁵⁾ Therefore, the proper management of catecholamine-infusion induced LVOT obstruction in ACS remains unclear.

The purpose of this study was to compare the effects of β -adrenoceptor blocker administration, α -adrenoceptor stimulator administration, and saline volume infusion on catecholamine-induced LVOT obstruction in a canine model of ACS.

METHODS

Animal preparation: Twenty-nine mongrel dogs (15-25 kg) were anesthetized with an initial intravenous injection of pentobarbital sodium (30 mg/kg) and ventilated with a Harvard respiratory pump set. A Swan-Ganz catheter was placed in the pulmonary artery via the right femoral vein, and a fluid-filled catheter was advanced into the ascending aorta from the right carotid artery. A midsternal thoracotomy was performed and the pericardium was incised. The institutional committee of Kagoshima University approved the study protocol and all procedures and euthanasia were performed while minimizing pain and distress to the animal according to National Institutes of Health Guidelines for Care and Use of Laboratory Animals.

Experimental protocol: The proximal portion of the left anterior descending coronary artery was ligated to induce ACS. Dobutamine infusion was started 30 minutes after the coronary artery ligation, and LVOT obstruction or the pressure gradient was monitored by continuous wave Doppler echocardiography [pressure gradient (mmHg) = $4 \times \text{velocity (m/sec)}^2$].⁸⁾ A commercially available phased array scanner (ALOKA SSD-5500, Tokyo) with a 3.5 MHz transducer was used for Doppler echocardiographic measurements. Dobutamine infusion was initiated at 10 $\mu\text{g/kg/min}$ and was gradually increased to 40 $\mu\text{g/kg/min}$ provided significant obstruction, defined as pressure gradient > 30 mmHg, did not occur. Twenty-one dogs with significant LVOT pressure gradients were used and 8 other dogs were excluded.

Dogs with significant LVOT obstruction were assigned to one of 3 groups:

group 1 ($n = 8$), in which the effects of propranolol infusion ($0.7\text{--}1.0 \mu\text{g/kg/min}$) were evaluated; group 2 ($n = 7$), in which the effects of phenylephrine ($10\text{--}200 \mu\text{g/kg/min}$) were evaluated; and group 3 ($n = 6$), in which the effects of saline infusion ($200\text{--}400 \text{ mL/hr}$) were evaluated.

Heart rate, blood pressure, pulmonary artery pressure, and cardiac output or stroke volume (determined by the thermodilution method) were assessed before and after the interventions. Hemodynamic data were recorded on an 8-channel chart recorder (Power Lab, AD Instruments, Sydney, Australia) and saved directly to a computer hard disk.

Statistics: All data are expressed as the mean $\pm$ SD. Within group data were compared by the paired Student's t test. Comparisons among groups were performed using analysis of variance (ANOVA). A P value < 0.05 was considered to represent statistical significance.

RESULTS

Effects of interventions on LVOT obstruction (Figure 1): Each intervention produced a similar decrease in LVOT obstruction, and there was no significant difference in the effect when comparing among interventions.

Effects of interventions on other hemodynamic variables (Table): Heart rate showed a significant decrease in response to propranolol infusion ($P < 0.01$), a slight but nonsignificant decrease with phenylephrine infusion, and did not change in

Figure 1. Effects of propranolol, phenylephrine infusion, and saline loading on the left ventricular outflow tract (LVOT) pressure gradient provoked by dobutamine infusion in the context of anteroapical acute myocardial infarction. All procedures achieved a similar reduction in the LVOT pressure gradient.

Table. Effects of Propranolol, Phenylephrine Infusion, and Saline Loading on Hemodynamics

	Propranolol (<i>n</i> = 8)			Phenylephrine (<i>n</i> = 7)			Saline Loading (<i>n</i> = 6)		
	pre	post		pre	post		pre	post	
HR (beats/min)	168 ± 34	148 ± 27	<i>P</i> < 0.01	164 ± 31	150 ± 16	NS	170 ± 18	169 ± 20	NS
LV diameter (mm)									
Dd	17 ± 1	21 ± 1	<i>P</i> < 0.01	17 ± 1	24 ± 2	<i>P</i> < 0.01	16 ± 1	24 ± 3	<i>P</i> < 0.01
Ds	7 ± 1	12 ± 2	<i>P</i> < 0.01	7 ± 1	11 ± 1	<i>P</i> < 0.01	5 ± 1	14 ± 4	<i>P</i> < 0.01
Aortic pressure (mmHg)									
Systolic	114 ± 11	130 ± 18	<i>P</i> < 0.05	118 ± 10	170 ± 38	<i>P</i> < 0.05	118 ± 32	134 ± 31	<i>P</i> < 0.05
Diastolic	62 ± 17	83 ± 28	<i>P</i> < 0.01	61 ± 13	101 ± 39	<i>P</i> < 0.05	72 ± 25	84 ± 27	NS
Mean	79 ± 13	99 ± 24	<i>P</i> < 0.01	80 ± 9	125 ± 34	<i>P</i> < 0.01	87 ± 27	101 ± 26	NS
Cardiac output (L/min)	1.3 ± 0.9	1.4 ± 1.0	NS	1.3 ± 0.9	1.6 ± 1.0	<i>P</i> < 0.05	2.1 ± 0.6	2.8 ± 1.2	<i>P</i> < 0.05
Stroke volume (mL/beat)	8 ± 6	9 ± 7	<i>P</i> < 0.05	8 ± 7	11 ± 7	<i>P</i> < 0.05	12 ± 3	16 ± 6	<i>P</i> < 0.05
LVOT pressure gradient (mmHg)	60 ± 16	15 ± 12	<i>P</i> < 0.001	68 ± 15	12 ± 10	<i>P</i> < 0.001	58 ± 18	22 ± 10	<i>P</i> < 0.001
PA pressure (mmHg)									
Systolic	28 ± 7	25 ± 4	NS	27 ± 8	31 ± 8	<i>P</i> < 0.05	23 ± 4	27 ± 5	<i>P</i> < 0.05
Diastolic	16 ± 5	11 ± 3	<i>P</i> < 0.05	12 ± 3	14 ± 3	NS	16 ± 4	17 ± 2	NS
Mean	20 ± 5	16 ± 3	NS	17 ± 4	19 ± 4	<i>P</i> < 0.05	18 ± 3	20 ± 2	NS

Dd indicates diastolic dimension; Ds, systolic dimension; HR, heart rate; LV, left ventricle; PA, pulmonary artery; and NS, not significant.

Figure 2. Effects of propranolol, phenylephrine infusion, and saline loading on systolic blood pressure in the presence of dobutamine-induced left ventricular outflow tract obstruction in the context of anteroseptal acute myocardial infarction. Phenylephrine infusion achieved a maximal increase in systolic blood pressure.

response to saline infusion. All interventions produced a significant increase in systolic and diastolic LV dimensions, with prominent increases both by phenylephrine infusion or saline loading. All interventions produced a significant elevation (*P* < 0.05) in systolic aortic pressure, with the greatest elevation occurring in

Figure 3. Effects of propranolol, phenylephrine infusion, and saline loading on cardiac output in the presence of dobutamine-induced left ventricular outflow tract obstruction in the context of antero-septal acute myocardial infarction. Saline loading achieved a maximal increase in cardiac output.

Figure 4. Effects of propranolol, phenylephrine infusion, and saline loading on diastolic pulmonary artery pressure in the presence of dobutamine-induced left ventricular outflow tract obstruction in the context of antero-septal acute myocardial infarction. Only propranolol infusion produced a significant decrease in diastolic pulmonary artery pressure.

response to phenylephrine infusion (Figure 2). Cardiac output did not change in response to propranolol administration, but was significantly increased by phenylephrine infusion and significantly and maximally increased by saline infusion ($P < 0.05$). All interventions produced a significant increase in stroke volume, with the maximal increase occurring in response to saline loading ($P < 0.01$, Figure 3). Systolic pulmonary artery pressure showed a significant increase in response to phenylephrine infusion and saline loading ($P < 0.05$) but decreased

slightly in response to propranolol administration. Diastolic pulmonary artery pressure showed a significant decrease in response to propranolol administration ($P < 0.05$), but did not change in response to the other interventions. Mean pulmonary artery pressure showed a significant increase in response to phenylephrine infusion ($P < 0.05$) (Figure 4) but did not change in response to the other interventions.

DISCUSSION

The present study demonstrated that all 3 interventions (propranolol, phenylephrine, and saline volume loading) were equally effective at reversing catecholamine-induced LVOT obstruction in an animal model of ACS. However, each intervention produced a different profile of hemodynamic changes. For example, propranolol administration resulted in decreased heart rate, elevated blood pressure, and reduced pulmonary artery pressure, while phenylephrine administration resulted in elevated blood pressure, decreased heart rate, and increased cardiac output, and saline volume loading resulted in increased cardiac output and elevated blood pressure.

Effects of propranolol: Previous studies have suggested that catecholamine-induced LVOT in the context of ACS resulted from compensative hyperkinesis of the nonischemic LVOT and the inferoposterior segment¹⁻⁵⁾ and that the negative inotropic effect of propranolol can attenuate the enhanced hyperdynamic motion of the nonischemic LV segments⁹⁾ and thereby result in reversal of LVOT obstruction.⁶⁾ Further, reversal of LVOT obstruction may induce a paradoxical increase in cardiac output and systemic blood pressure and thereby decrease diastolic LV filling pressure and pulmonary artery pressure.¹⁰⁾ Based on these properties, propranolol may be useful in the management of pulmonary congestion with LVOT obstruction in ACS.

Effects of phenylephrine: Phenylephrine-induced peripheral vasoconstriction results in an increase in aortic pressure and ventricular loading,¹¹⁾ thereby reducing the hyperdynamic motion of nonischemic myocardium and relieving LVOT obstruction.^{6,7)} Further, phenylephrine administration resulted in an increase in pulmonary artery pressure in the present study. In principle, the increase in afterload and the constriction of pulmonary vessels can result in an increase in pulmonary artery pressure.^{10,12)} In the present study, systolic maximal LV pressure, calculated as the sum of the maximal aortic pressure and the LVOT pressure gradient, did not increase significantly in response to phenylephrine. Therefore, the elevation in pulmonary artery pressure may result from a phenylephrine-induced increase in pulmonary vessel contraction rather than an increase in afterload to the LV. Further, reversal of LVOT obstruction may result in a paradoxical

increase in cardiac output via α -stimulation. Based on these properties and the fact that the greatest increase in aortic pressure occurred in response to phenylephrine, phenylephrine may be useful in the management of hypotension associated with LVOT obstruction in ACS.

Effects of saline loading: Saline volume loading increases preload and LV size,¹⁵⁾ thereby reversing LVOT obstruction. Increases in cardiac output may result from increases in preload, which is consistent with observations from the present study demonstrating that saline loading produced the maximal increase in cardiac output. Regarding pulmonary congestion, however, saline loading potentially has 2 opposing effects: 1) the attenuation of pulmonary congestion by reducing LVOT obstruction and afterload to the LV and 2) the worsening of pulmonary congestion by increasing preload to the LV. Therefore, it is expected that saline volume loading can be effective for low output syndrome associated with LVOT obstruction and AMI. However, this intervention requires careful consideration due to the possibility of worsening pulmonary congestion.

Relationship to previous studies and clinical implications: The importance of LVOT obstruction has been demonstrated from multiple aspects.¹³⁻¹⁵⁾ The present study confirmed these reports by showing hemodynamic improvement after relief of the LVOT obstruction. Previous studies¹⁻⁵⁾ have also suggested that decreasing the rate or completely discontinuing catecholamine infusion was not necessarily effective in reversing catecholamine-induced LVOT obstruction. However, the present study demonstrated that a β -adrenoceptor antagonist, an α -adrenoceptor agonist, and saline loading were effective in reversing catecholamine-induced LVOT obstruction, which is consistent with observations from previous studies.^{6,7)} Further, the results of the present study demonstrate that β -adrenoceptor antagonists may be preferred in the context of pulmonary congestion, while α -adrenoceptor agonists may be preferred in the context of hypotension, and that saline loading may be preferred in the context of a low output syndrome.

The important influences of the geometry of the mitral valve complex on leaflet function have been shown in patients with ischemic mitral regurgitation and restricted leaflet closure¹⁶⁻²⁰⁾ and also in those with systolic anterior motion of the mitral valve and an excessive leaflet closing motion toward the LVOT.^{21,22)} The present findings confirmed the important influence of the mitral valve complex on LVOT obstruction by demonstrating that interventions to promote LV dilatation attenuated LVOT obstruction.

Limitations: The study possesses several notable limitations. First, the dose of dobutamine required to induce LVOT obstruction in dogs was higher than typically required to induce LVOT obstruction in clinical practice. Second, the effects of discontinuing or reducing the dose of dobutamine infusion were only assessed in 2 dogs. Discontinuation of the drug in these animals resulted in a decrease in

blood pressure and cardiac output despite relief of LVOT obstruction, which is consistent with clinical studies¹⁻⁵⁾ and suggests that discontinuation of the agent alone does not result in optimal outcomes.

Conclusions: Propranolol, phenylephrine infusion, and saline volume loading were similarly effective at reversing dobutamine-induced LVOT obstruction in a canine model of ACS. However, each intervention produced different hemodynamic effects and may have different clinical indications.

REFERENCES

1. Armstrong WF, Marcovitz PA. Dynamic left ventricular outflow tract obstruction as a complication of acute myocardial infarction. *Am Heart J* 1996; 131: 827-30.
2. Haley JH, Sinak LJ, Tajik AJ, Ommen SR, Oh JK. Dynamic left ventricular outflow tract obstruction in acute coronary syndromes: an important cause of new systolic murmur and cardiogenic shock. *Mayo Clin Proc* 1999; 74: 901-6.
3. Joffe II, Riley MF, Katz SE, Ginsburg GS, Douglas PS. Acquired dynamic left ventricular outflow tract obstruction complicating acute anterior myocardial infarction: serial echocardiographic and clinical evaluation. *J Am Soc Echocardiogr* 1997; 10: 717-21.
4. Bartunek J, Vanderheyden M, de Bruyne B. Dynamic left ventricular outflow tract obstruction after anterior myocardial infarction. A potential mechanism of myocardial rupture. *Eur Heart J* 1995; 16: 1439-42.
5. Hrovatin E, Piazza R, Pavan D, *et al.* Dynamic left ventricular outflow tract obstruction in the setting of acute anterior myocardial infarction: a serious and potentially fatal complication? *Echocardiography* 2002; 19: 449-55.
6. Flamm MD, Harrison DC, Hancock EW. Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. *Circulation* 1968; 38: 846-58.
7. Stewart WJ, Schiavone WA, Salcedo EE, Lever HM, Cosgrove DM, Gill CC. Intraoperative Doppler echocardiography in hypertrophic cardiomyopathy: correlations with the obstructive gradient. *J Am Coll Cardiol* 1987; 10: 327-35.
8. Hatle L, Brubakk A, Tromsdal A, Angelsen B. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. *Br Heart J* 1978; 40: 131-40.
9. Coltart J, Alderman EL, Robison SC, Harrison DC. Effect of propranolol on left ventricular function, segmental wall motion, and diastolic pressure-volume relation in man. *Br Heart J* 1975; 37: 357-64.
10. Jebavy P, Koudelkova E, Henzlova M. Unloading effects of prazosin in patients with chronic aortic regurgitation. *Am Heart J* 1983; 105: 567-74.
11. Otsuji Y, Tei C, Kisanuki A, Natsugoe K, Kawazoe Y. Color Doppler echocardiographic assessment of the change in the mitral regurgitant volume. *Am Heart J* 1987; 114: 349-54.
12. Fike CD, Aschner JL, Zhang Y, Kaplowitz MR. Impaired NO signaling in small pulmonary arteries of chronically hypoxic newborn piglets. *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L1244-54.
13. Tsuchikane E, Takeda Y, Kobayashi T, *et al.* Percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy. *Circ J* 2003; 67: 763-7.
14. Konishi C, Shiraishi J, Muraguchi N, *et al.* Beneficial effect of cibenzoline on left ventricular pressure gradient with sigmoid septum. *Circ J* 2004; 68: 968-71.
15. Nomura T, Harada Y, Suzuki Y, *et al.* Left ventricular outflow tract obstruction due to anomalous insertion of papillary muscle. *Circ J* 2004; 68: 1219-22.
16. Zhou X, Otsuji Y, Yoshifuku S, *et al.* Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular regurgitation. *Circ J* 2002; 66: 913-6.
17. Takagaki M, McCarthy PM, Goormastic M, *et al.* Determinants of the development of mitral regurgitation in pacing-induced heart failure. *Circ J* 2003; 67: 78-82.

18. Otsuji Y, Handschumacher MD, Schwammenthal E, *et al.* Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct *in vivo* demonstration of altered leaflet tethering geometry. *Circulation* 1997; 96: 1999-2008.
19. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: A quantitative clinical study. *Circulation* 2000; 102: 1400-6.
20. Arikawa K, Otsuji Y, Zhang H, *et al.* Left ventricular remodeling is less while left atrial remodeling is greater in inferior compared to anterior myocardial infarction: importance of ischemic mitral regurgitation. *J Echocardiogr* 2004; 2: 43-8.
21. Levine RA, Vlahakes GJ, Lefebvre X, *et al.* Papillary muscle displacement causes systolic anterior motion of the mitral valve. Experimental validation and insights into the mechanism of subaortic obstruction. *Circulation* 1995; 91: 1189-95.
22. Sakurai S, Tanaka H, Yoshimura H, Nakao S, Tahara M. Production of systolic anterior motion of the mitral valve in dogs. *Circulation* 1985; 71: 805-12.