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

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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 µg/kg/min). Subsequently, the effects of propranolol infusion (0.7 to 1.0 µg/kg/min, n = 8), phenylephrine infusion (10 to 200 µg/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 = NS for comparison between interventions). Phenylephrine produced the greatest elevation in aortic pressure (propranolol: +15 ± 13; phenylephrine: +51 ± 36; saline loading: +15 ± 15 mmHg; P < 0.05), while saline loading produced the greatest increase in cardiac output (propranolol: +0.05 ± 0.12; phenylephrine: +0.28 ± 0.37; saline loading: +0.73 ± 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
LEFT ventricular outflow tract (LVOT) obstruction may occur in response to catecholamine infusion in patients with acute coronary syndrome (ACS), thereby resulting in serious hemodynamic deterioration. Previous reports have demonstrated that administration of a β-adrenoceptor blocker or an α-adrenergic stimulator, and avoidance of hypovolemia 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. 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 × velocity (m/sec)²]. 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 µg/kg/min and was gradually increased to 40 µg/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 (0.7-1.0 \( \mu g/kg/min \)) were evaluated; group 2 \( (n = 7) \), in which the effects of phenylephrine (10-200 \( \mu g/kg/min \)) were evaluated; and group 3 \( (n = 6) \), in which the effects of saline infusion (200-400 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 anteroseptal acute myocardial infarction. All procedures achieved a similar reduction in the LVOT pressure gradient.](image-url)
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

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

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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 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 segment\(^1-^5\) and that the negative inotropic effect of propranolol can attenuate the enhanced hyperdynamic motion of the nonischemic LV segments\(^9\) 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 $\alpha$-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, 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. The present study confirmed these reports by showing hemodynamic improvement after relief of the LVOT obstruction. Previous studies 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 $\beta$-adrenoceptor antagonist, an $\alpha$-adrenoceptor agonist, and saline loading were effective in reversing catecholamine-induced LVOT obstruction, which is consistent with observations from previous studies. Further, the results of the present study demonstrate that $\beta$-adrenoceptor antagonists may be preferred in the context of pulmonary congestion, while $\alpha$-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 closure and also in those with systolic anterior motion of the mitral valve and an excessive leaflet closing motion toward the LVOT. 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 studies\textsuperscript{1-5} 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**


