Experimental Studies

Effects of Propranolol on Coronary Vasculature and Cardiac Performance in Dogs with Fixed and Dynamic Coronary Stenosis

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SUMMARY

The coronary hemodynamic effects of propranolol (0.1 mg/kg, i.v.) were examined in anesthetized dogs with flow-limiting dynamic and fixed coronary stenosis of the left circumflex coronary artery. During fixed coronary stenosis created by external application of an occluder device, propranolol significantly decreased coronary blood flow (CBF) by 6.8± 2.7% (mean±SEM, $p<0.05$) and increased mean distal coronary pressure (DCP) by 7±2.1 mmHg ($p<0.05$). This resulted in a decrease in stenosis resistance (SR) by 26±3.1% ($p<0.01$) due to oxygen demand reduction. By contrast, during dynamic coronary stenosis produced by an intraluminal microballoon occluder, propranolol decreased CBF by 68± 3.4% ($p<0.01$) and mean DCP by 36±4.2 mmHg ($p<0.01$), resulting in an increase in SR by 694±109% ($p<0.01$). This increase in SR was attenuated by pretreatment with an alpha-adrenergic receptor antagonist phentolamine (0.5 mg/kg, i.v.), or by holding heart rate constant at the pretreatment level.

These results suggest that propranolol ameliorated the severity of stenosis during fixed coronary stenosis and exacerbated the severity during dynamic coronary stenosis. This increase in SR appears to be related to vasoconstriction of the large stenosed coronary artery, mediated both by alpha-adrenergic receptors in the coronary artery and by myocardial oxygen demand reduction.

Additional Indexing Words:

Coronary stenosis Propranolol Vasoconstriction Phentolamine Atrial pacing

BETA-ADRENERGIC receptor blockade effectively alleviates the symptoms of patients with effort angina pectoris.[1),2)] Nevertheless, this agent was found to have little effect on the alleviation of symptoms in patients whose angina is mainly induced by coronary artery spasm.[3),4)] The patho-

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genesis of angina pectoris is believed to be based on fixed and dynamic obstruction and an increase in large epicardial coronary arterial tone may trigger or aggravate myocardial ischemia in many patients with angina pectoris.[5] To investigate the mechanisms of variable responses to propranolol of patients with different anginal syndromes, we employed 2 experimental models of coronary stenosis: one that preserved stenosis vasomobility (referred to here as dynamic coronary stenosis) and one that precluded it (fixed coronary stenosis). These models were used to assess the effects of intravenous injections of propranolol on coronary vasculature and cardiac performance.

Methods

Studies were conducted on adult mongrel dogs weighing between 11 and 16 kg. Dogs were premedicated with morphine sulfate (1 mg/kg) and anesthetized with alpha chloralose (100 mg/kg, i.v.). They were intubated and ventilated by a respirator using air supplemented with oxygen. Blood gases and acid / base balance were maintained within normal limits. A left thoracotomy was performed through the fifth intercostal space and the heart was supported in a pericardial cradle. Aortic pressure was measured by a catheter situated in the aortic arch. A polyethylene catheter was placed in a small branch of the circumflex coronary artery for measurement of distal coronary pressure (DCP). A stiff catheter, 10 cm long, was inserted into the left ventricle through the apex to record left ventricular (LV) pressure and its first

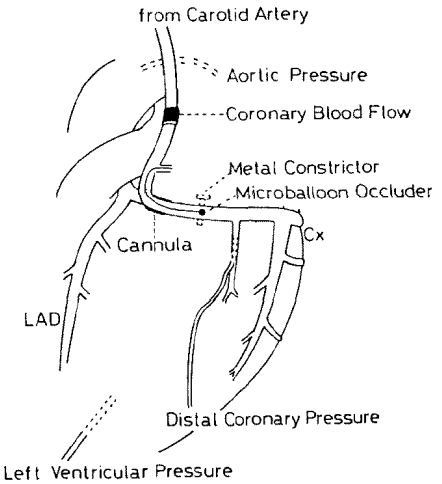

Fig. 1. Experimental preparation. LAD=left anterior descending artery; Cx=left circumflex coronary artery.

derivative (LV dP/dt). The left common carotid artery was exposed and the circumflex coronary artery was dissected free close to its origin. After administration of 5,000 units of heparin, the circumflex artery was ligated, cannulated distally with a thin metal cannula (2.4 mm i.d.) and perfused continuously from the left carotid artery through the perfusion tubing with a minimal internal diameter of 2.4 mm (Fig. 1). The adequacy of this perfusion system was indicated by preservation of an autoregulatory reserve greater than a 300% peak reactive hyperemic response after a 15 sec total coronary occlusion in each dog.[6] Heparin (2,000 units) was supplemented every 30 min. Coronary blood flow (CBF) was measured with a precalibrated extracorporeal electromagnetic flow probe. Pressures were measured with Statham transducers (P23Db). Measurements of heart rate, aortic pressure, LV pressure, LV dP/dt, LV end-diastolic pressure (LVEDP), DCP and CBF were recorded continuously. The preparation was allowed to stabilize for at least 30 min after coronary cannulation.

Fixed coronary stenosis was produced by external application of a constrictor device. The proximal portion of the circumflex artery distal to the perfusion cannula was dissected free and a screw-type metal constrictor was placed around the artery to produce a pressure gradient across the stenosis. Dynamic coronary stenosis was produced with a specially-made balloon occluder, consisting of a miniature rubber balloon attached to the tip of a polyethylene tube (0.6 mm external diameter). The construction of the microballoon occluder and the characteristics of the experimental model were reported previously.[7] This occluder was inserted through the side arm of the perfusion tubing and advanced into the intact proximal portion of the left circumflex artery. It was ascertained that the placement of the occluder in the coronary artery affected neither the resting coronary blood flow, its phasic pattern nor the peak reactive hyperemic response. The size of the balloon was adjusted by infusing saline to obtain a pressure gradient across the stenosis; the expansion volume was kept constant. Application of stenosis produced a pressure gradient of approximately 25–30 mmHg. Stenosis resistance (SR) was calculated by dividing the mean pressure gradient across the stenosis by the mean CBF. The mean pressure gradient was calculated as the mean aortic pressure minus the mean DCP.

Intravenous injection of propranolol (0.1 mg/kg) was performed in 21 dogs prepared as described above: 7 with dynamic coronary stenosis, 7 with fixed coronary stenosis and 7 without coronary stenosis. In the ischemic series, coronary stenosis was produced after control resting recording. For each condition, a 10 min stabilization period elapsed before the intravenous injection of propranolol was performed over 2 min. All hemodynamic mea-

surements were made continuously during the control condition, coronary stenosis, drug infusion and 10 min after cessation of the infusion. In 7 dogs, the effects of propranolol on dynamic coronary stenosis were studied with heart rate held constant at the pretreatment level by means of atrial pacing. Another 7 dogs were pretreated with phentolamine (0.5 mg/kg, i.v.).

Statistical analysis:

The mean and standard error of the mean (SEM) were calculated for all variables. Data for each animal were analyzed by t-tests for paired comparisons. The responses to propranolol under varied conditions were compared using analysis of variance and Tukey's test.

Results

There were no significant differences between initial control measurements from dogs in the different experimental groups. Similarly, there was no difference in these parameters as a function of the method of inducing coronary stenosis.

The systemic hemodynamic effects of propranolol in different experimental conditions are shown in Table I. Propranolol produced nearly identical decreases in heart rate and LV dP/dt, without significantly affecting either mean aortic pressure or LVEDP in the 3 groups. In dogs without coronary stenosis, propranolol decreased the heart rate by 25 ± 2.1 beats/min, the LV dP/dt by 450 ± 72 mmHg/sec and the CBF by $18\pm1.7\%$, respectively. The coronary hemodynamic effects of propranolol, though, differed as a function of dynamic or fixed coronary stenosis (Figs. 2 and 3). Application of fixed and dynamic coronary stenosis decreased the CBF by 18 ± 1.8 and $20\pm1.7\%$ and the mean DCP by 27 ± 3.7 and 27 ± 1.8 mmHg, respectively. During fixed coronary stenosis, propranolol increased the mean DCP by 7 ± 2.1 mmHg and decreased CBF by $6.8\pm2.7\%$ and SR by $26\pm3.1\%$. By contrast, propranolol administration during dynamic coronary stenosis decreased the CBF by $68\pm3.4\%$ and the mean DCP by 36 ± 4.2 mmHg and increased the SR by $694\pm109\%$.

Intravenous injection of phentolamine reduced the mean aortic pressure by 6 ± 1.1 mmHg ($p<0.05$) and increased the heart rate by 11 ± 2.6 beats/min ($p<0.05$). Other parameters were not changed significantly. In dogs with dynamic coronary stenosis, propranolol in the presence of phentolamine reduced the heart rate by 34 ± 5.0 beats/min and the LV dP/dt by 743 ± 149 mmHg/sec. In this condition, propranolol also decreased both the CBF by $49\pm4.7\%$ and the mean DCP by 25 ± 3.4 mmHg and increased the SR by

Table I. Systemic Hemodynamic Effects of Propranolol on Fixed and Dynamic Stenosis Models

	Heart rate (beats/min)	Mean aortic pressure (mmHg)	LV pressure systolic (mmHg)	LV pressure end-diastolic (mmHg)	LV dP/dt (mmHg/sec)
Without stenosis					
Preinjection	132 (3.7)	102 (5.6)	125 (5.8)	6 (0.7)	2639 (147)
Propranolol	107 (2.4)**	101 (5.7)	124 (5.8)	6 (1.1)	2189 (173)**
Fixed stenosis					
Preocclusion	131 (5.6)	99 (6.8)	123 (7.0)	7 (0.7)	2443 (186)
Preinjection	130 (5.3)	99 (6.9)	123 (7.1)	7 (0.7)	2429 (178)
Propranolol	107 (5.7)**	97 (6.9)	119 (7.7)	8 (0.8)	2056 (195)**
Dynamic stenosis					
Preocclusion	132 (3.4)	98 (3.6)	121 (4.7)	6 (0.7)	2407 (159)
Preinjection	131 (3.4)	99 (4.2)	121 (4.5)	7 (0.7)	2047 (159)
Propranolol	105 (3.4)**	97 (4.1)	118 (4.2)	8 (1.1)	1943 (170)**
Dynamic stenosis (pretreatment with phentolamine)					
Preocclusion	138 (6.5)	99 (7.5)	123 (8.4)	6 (1.2)	2771 (186)
Preinjection	138 (6.5)	97 (7.6)	122 (8.6)	7 (1.0)	2743 (172)
Propranolol	104 (3.3)**	96 (7.4)	119 (8.8)	8 (1.5)	2000 (172)**
Dynamic stenosis (heart rate held constant)					
Preocclusion	130 (10.1)	98 (6.4)	120 (7.4)	6 (0.6)	2350 (123)
Preinjection	132 (10.2)	97 (6.7)	119 (7.9)	7 (0.7)	2301 (132)
Propranolol	130 (9.4)	96 (7.2)	116 (8.3)	8 (0.4)	1744 (98)**

Values are mean (SEM). LV = left ventricular.
** Compared to above $p < 0.01$.

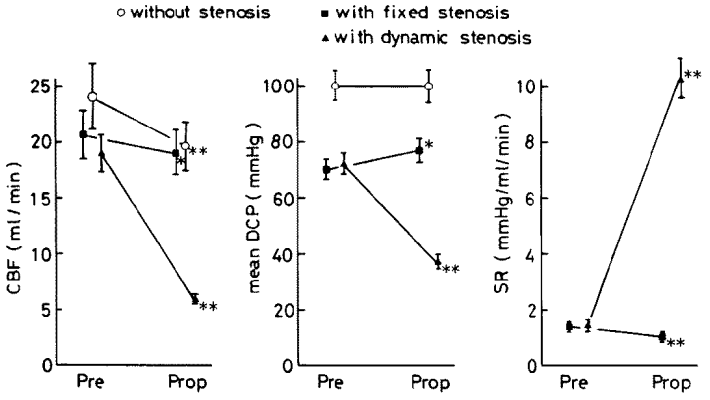

Fig. 2. Effects of propranolol (Prop) on coronary blood flow (CBF), mean distal coronary pressure (DCP) and stenosis resistance (SR) in different experimental conditions. * $p < 0.05$, ** $p < 0.01$ compared to preinjection (Pre).

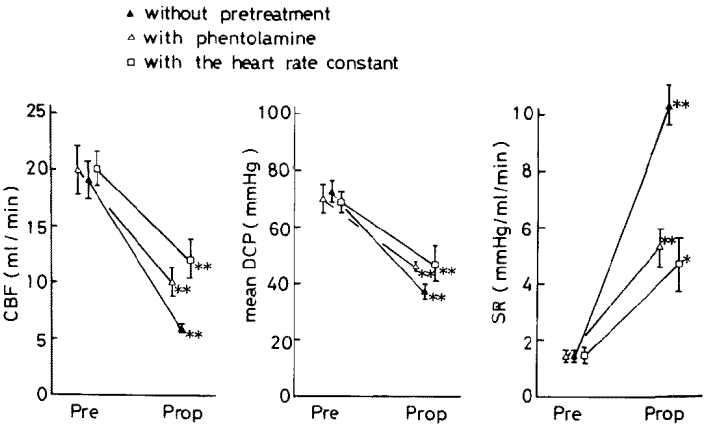

Fig. 3. Effects of propranolol (Prop) on coronary blood flow (CBF), mean distal coronary pressure (DCP) and stenosis resistance (SR) during dynamic coronary stenosis. * $p<0.05$, ** $p<0.01$ compared to preinjection (Pre).

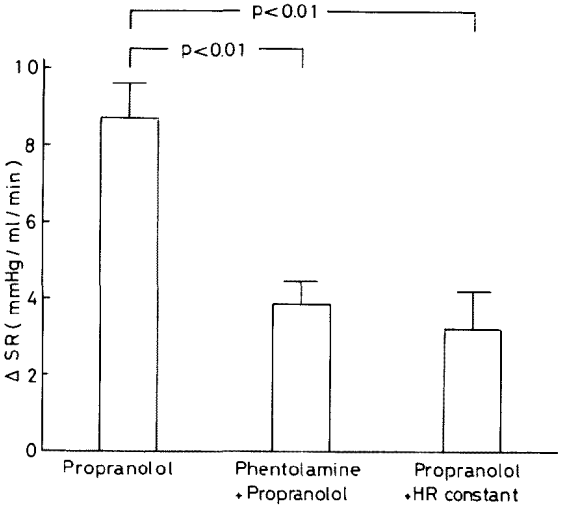

Fig. 4. Changes in stenosis resistance (ΔSR) in responses to propranolol during dynamic coronary stenosis. HR=heart rate.

288±42%. In dogs with the heart rate held constant at the pretreatment level, intravenous propranolol during dynamic coronary stenosis decreased the CBF by 38±8.5%, and the mean DCP by 22±3.3 mmHg and increased the SR by 284±103%. Finally, the increase in the SR during dynamic coronary stenosis was attenuated by pretreatment with alpha-adrenergic blockade or by holding heart rate constant at the pretreatment level (Fig. 4).

Discussion

The results of this study indicate that the effects of propranolol on coronary vasculature vary with the experimental model of coronary stenosis. Dogs with dynamic coronary stenosis respond differently to propranolol than dogs with fixed coronary stenosis. We have developed experimental models of coronary stenosis which are relevant to the clinical situation to examine the effects of antianginal agents on coronary circulation.[7)-10)] In most animal studies coronary stenosis is produced by the external application of an arterial occluder, which prevents active vasomotion, or by the occlusion of noncompliant perfusion tubing. In these fixed coronary stenosis models, vasodilatory agents such as nitroglycerin have failed to either alter the SR or to augment the CBF through a stenosed artery. Thus, we developed a new model of coronary stenosis produced by intraluminal coronary obstruction with an inflation of a microballoon placed within the proximal coronary artery. This model preserved active vasomotion of a stenosed segment and has been termed dynamic coronary stenosis. During dynamic coronary stenosis, nitroglycerin caused a marked reduction in the SR, an increase in the CBF and eliminated myocardial ischemia evoked by ergonovine.[7),9)]

In the absence of coronary stenosis, propranolol decreased the heart rate, the LV dP/dt and the CBF by decreasing the oxygen demand. In animal studies, propranolol has lowered the calculated severity of coronary stenosis, which was created with the mechanical occluder around the coronary artery. This effect appeared to be mediated by autoregulatory increases in distal bed vascular resistance and DCP, due to a decrease in myocardial oxygen demand associated with the negative chronotropic and inotropic effects.[11),12)] Our data from a fixed coronary stenosis model are consistent with these reports. In the presence of fixed coronary stenosis, a reduced myocardial oxygen demand elicited constriction of small coronary arteries, resulting in increased mean DCP and a passive reduction of the SR. These results may correspond with the alleviation of symptoms in patients with effort angina pectoris.

In contrast, propranolol increased the SR during dynamic coronary stenosis. Several mechanisms of this increased SR were considered. First, it is likely that there is vasoconstriction of the large stenosed coronary artery mediated by alpha-adrenergic receptors. *In vitro* studies indicate that alpha-adrenergic receptors are located preferentially in the proximal portion of coronary arterial trees.[13)] In anesthetized and conscious dogs, alpha-adrenergic receptor stimulation has increased the coronary vascular resistance and reduced the large coronary artery diameter.[14)-16)] Clinically, alpha-adrenergic stimulation exacerbates the symptoms in patients with variant angina, effort

angina and myocardial infarction.[4),17),18)] In the present study, the propranolol-induced SR increase was attenuated by pretreatment with phentolamine. Vatner et al reported that beta-adrenergic receptor blockade decreased mean external left circumflex coronary artery diameter in the normal coronary circulation of conscious dogs.[19),20)] However, they suggested that the mechanisms of the constriction were unrelated to unopposed alpha-adrenergic receptor tone.[20)] The discrepancy between our results and the latter study may be attributed to the presence of coronary stenosis. The contribution of large coronary vessels to total coronary vascular resistance in normal arteries is small (less than 5%). In the presence of severe coronary stenosis, though, alterations in large epicardial arterial tone may be crucial in the regulation of coronary circulation.[21)]

The possibility of vasoconstriction of the large stenosed coronary artery, due to reduced myocardial oxygen demand, must also be considered. Vatner et al observed that beta-adrenergic stimulation increased the mean external left circumflex coronary diameter and that beta adrenergic receptor blockade produced the opposite effect.[19),20)] They suggested that these changes were $beta_1$-adrenergic effects. In the present study, the propranolol-induced SR increase was attenuated when the heart rate was paced at the pretreatment level. The negative chronotropic effect of propranolol appeared to be important in this condition. Although propranolol has been reported to inhibit the reduction of subendocardial contractility that is induced by coronary constriction, this effect was not observed when the heart rate was fixed.[22)]

Finally, there is the possibility that vasoconstriction of the large stenosed coronary artery is due to a direct constrictor effect of propranolol on vascular muscle. *In vitro* studies have shown that contraction of coronary arteries may be a direct effect of propranolol.[23)] In the present study, the propranolol-induced SR increase was attenuated by pretreatment with phentolamine or by pacing the heart rate at the pretreatment level. Thus, a direct effect of propranolol did not appear to be a major mechanism of the constriction.

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