Comparative Effects of Arotinolol, Labetalol and Propranolol on Regional Myocardial Dysfunction Induced by Flow-Limiting Coronary Stenosis in Anesthetized Dogs

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Abstract—Effects of arotinolol, a combined alpha- and beta-adrenoceptor blocking agent, on regional myocardial dysfunction produced by severe coronary stenosis in anesthetized dogs were examined and compared with those of labetalol and propranolol. Doses of these three antagonists were selected to produce a comparable degree of the negative chrono- and inotropic effect but a different potency of alpha-adrenoceptor blockade (labetalol > arotinolol). Regional myocardial function measured as segment shortening (%SS) was decreased to around 2–3% by constriction of the left circumflex coronary artery (LCX), and then drug or saline was administered i.v. The stenosis of LCX was released 30 min after the administration. No significant alteration in hemodynamic and contractility parameters was seen as compared to the predrug value up to at least 30 min after saline i.v. Arotinolol and propranolol both reduced heart rate and peak positive left ventricular dP/dt (LVdP/dt) without a significant change in LCX flow. Concomitantly, %SS distal to a coronary stenosis was significantly improved by arotinolol and propranolol. On the other hand, labetalol significantly reduced LCX flow probably due to systemic hypotension and failed to improve %SS in the ischemic area, although the agent markedly decreased heart rate and LVdP/dt. These results indicate that arotinolol improves impaired regional myocardial function distal to a coronary stenosis in a similar manner with propranolol.

Arotinolol, (±)-2-(3-tert-butylamino-2-hydroxypropylthio)-4-(5-carbamoyl-2-thienyl) thiazole hydrochloride, is a new non-selective beta-adrenoceptor antagonist that lacks an intrinsic sympathetic action and a membrane stabilizing action, and is additionally endowed with an alpha-adrenoceptor blocking property (1-3). The beta-adrenoceptor blocking effect of the agent in in vivo preparations is reported to be 9 times more potent that of propranolol and 30 times more potent that of labetalol, a typical combined alpha- and beta-adrenoceptor blocking drug (4), while the alpha-adrenoceptor blocking effect of arotinolol is reported to be 4–5 times less potent than that of labetalol (1, 2, 5). Classical beta-adrenoceptor blockers such as propranolol are widely used in the management of not only essential hypertension but also ischemic heart disease. Although antihypertensive effects of arotinolol have been demonstrated both in experimental models of hypertension (6) and in patients with essential hypertension (7, 8), the effect of this agent on myocardial ischemia has not yet been well-documented.

In this study, the effects of arotinolol on hemodynamics and regional dysfunction in a dog model of myocardial ischemia produced by flow-limited coronary stenosis were investigated and compared with those of labetalol and propranolol.
Materials and Methods

Thirty-two mongrel dogs of either sex weighing 11–20 kg were used. Dogs were anesthetized with sodium pentobarbital (25 mg/kg, i.v.), intubated, and ventilated with a Harvard respirator (model 607). The experimental model employed in this study was almost the same as the previously described one (9, 10). A left thoracotomy was performed through the fifth intercostal space. The pericardium was opened, and the heart was suspended in a pericardial cradle. The left circumflex coronary artery (LCX) was dissected free from the connecting tissue near its origin, and a snare-type occluder was placed around it. A heparin-filled catheter was introduced through the left carotid artery into the aortic root and connected to a Statham pressure transducer (P231D) to measure the aortic pressure. A catheter-tip manometer (Millar, PC-350) was inserted through the left femoral artery into the left ventricle to measure the left ventricular pressure. An appropriately sized electromagnetic flow probe (Statham, SP-7515) was placed around the LCX just proximal to the occluder and connected to an electromagnetic flowmeter (Statham, SP-2204) for the measurement of coronary blood flow.

Segment length measurements were obtained by activating the implanted piezoelectric crystals using sonomicrometry (11). Two pairs of 5 MHz ultrasonic crystals (2 mm in diameter) were positioned in the endocardium of the left ventricular free wall approximately 10 mm apart in a circumferential plane. One pair of crystals was placed in the wall within the distribution of the LCX, and another pair was placed in the anterior wall in the region perfused by the LCX (LAD). The leads of each crystal were connected to an ultrasonic system (MECC, UDM-5B) which transformed the acoustic impulse transmitted between the two crystals into an electronic signal proportional to the distance between the paired crystals. End-diastolic segment length (EDL) was determined just before the onset of the upstroke of left ventricular dP/dt (LVdP/dt). End-systolic segment length (ESL) was taken at 20 msec prior to peak negative LVdP/dt. Percent segment shortening (%SS), an index of regional myocardial function, was defined as EDL minus ESL divided by EDL multiplied by 100. A minimum of ten beats was averaged for each determination of regional function. Myocardial segment shortening measured by this method as an index of regional systolic function has been widely available to estimate the degree of localized myocardial ischemia since the 1970s (11). LVdP/dt was derived by differentiating the left ventricular pressure signal using an electronic differentiator (Nihon Kohden, ED-601G). Heart rate was continuously counted with a cardiotachometer (Nihon Kohden, AT-600G) triggered by the pressure pulse. Mean coronary blood flow was obtained by using an electronic resistance-capacitance filter with a 2 sec time constant. Data were continuously recorded on an eight-channel pen recorder (Nihon Kohden, WT-685G) and simultaneously stored on a magnetic tape (Sony, A47) for subsequent data analysis.

Experimental protocol: Experiments were started after a stabilization period of at least 30 min. Control hemodynamics and regional myocardial shortening were measured. The LCX was then gradually constricted with the occluder following administration of heparin (200 U/kg, i.v.), and a stenosis of the LCX was made sufficient to reduce resting coronary blood flow and to decrease %SS in the region perfused by the LCX to around 2–3%. In this situation, the LCX-perfused myocardium is nearly but not completely disabled for the active shortening due to the insufficient blood supply to this area. When hypofunction in the LCX area could not be obtained, probably due to an abundant collateral blood supply, the data were discarded. Around 30 min after the beginning of coronary stenosis, arotinolol (0.05 mg/kg, n=6; 0.1 mg/kg, n=6), labetalol (0.1 mg/kg, n=6), propranolol (0.2 mg/kg, n=6) or physiological saline (0.9% NaCl; 0.3 ml/kg, n=8) was administered intravenously. Constriction of the LCX was released 30 min after the drug administration. Doses of arotinolol, labetalol and propranolol were selected to produce a similar degree of the negative chrono- and inotropic effect by considering the results obtained in preliminary experi-
ments. Labetalol at the dose employed in this study was expected to have a more potent alpha-adrenoceptor blocking activity than arotinolol (0.05 or 0.1 mg/kg). To test the efficacy of alpha- and beta-blockade, responses to phenylephrine (2 μg/kg, i.v.) and (-)-isoproterenol (100 ng/kg, i.v.) before stenosing were respectively compared with those obtained 40–45 min after administration of these agents.

**Drugs:** The following drugs were used: arotinolol hydrochloride (S-596, Sumitomo Pharmaceuticals), labetalol hydrochloride (Glaxo), propranolol hydrochloride (ICI), phenylephrine hydrochloride (Kowa) and (-)-isoproterenol hydrochloride (Nikken Kagaku). All drugs were dissolved in physiological saline.

**Statistical analysis:** All data were expressed as a mean±S.E.M. Within each treatment, comparisons of the changes with time were made using an analysis of variance. Dunnett’s test was used for multiple comparisons. Comparisons between treatment and vehicle were made using by Student’s t-test. Paired data were analyzed by a paired t-test. P values of less than 0.05 were considered to be statistically significant.

**Results**

Changes in hemodynamics and regional myocardial shortenings after coronary stenosis: Partial constriction of the LCX resulted in reductions in the LCX flow to 38–53% of the resting flow, and allowed the LCX-perfused myocardium to impair segment shortenings to 2.1–3.0% (Tables 1 and 2). Impairment of regional function was associated with significant increases in LVEDP and segment shortenings in the LAD-perfused region in all groups (Tables 1 and 2). These altered parameters caused by coronary constriction as well as other hemodynamic variables such as mean aortic pressure, (+)LVDp/dt and heart rate appeared stable during stenosis until at least 30 min after administration of vehicle (Tables 1 and 2).

Effects of arotinolol, labetalol and propranolol on hemodynamic variables and regional myocardial function during coronary stenosis: A representative tracing from a dog receiving arotinolol 0.05 mg/kg, i.v., is demonstrated in Fig. 1. Arotinolol apparently reduced both heart rate and (+)LVDp/dt in a weak dose-related manner (Table 1). Similarly, both labetalol and propranolol decreased these two parameters (Table 1, Fig. 2). Although slight hypotension was seen after each administration of arotinolol at two doses and propranolol, the LCX flow was not significantly affected by these agents as well as vehicle administration (Table 1). Labetalol immediately lowered the mean aortic pressure by 19±2% of the predrug value and produced a significant reduction in LCX flow. Left ventricular end-diastolic pressure significantly rose following administration of all drugs except for the higher dose of arotinolol. As seen in Fig. 2, percent changes in heart rate, (+)LVDp/dt and calculated rate-pressure product were immediately and continuously decreased by all these agents but not by the vehicle.

Changes in myocardial segment shortening seen in the groups administered the vehicle, arotinolol (0.05 mg/kg and 0.1 mg/kg), labetalol and propranolol are summarized in Table 2. End-diastolic lengths in both LAD- and LCX-perfused regions significantly increased after administration of these beta-blockers except for the higher dose of arotinolol, probably reflecting rises in left ventricular end-diastolic pressure. Segment shortenings in the ischemic (LCX-perfused) region during coronary stenosis were increased by both doses of arotinolol and propranolol, but these were not significantly altered by vehicle nor by labetalol. The changes from the predrug value in segment shortenings caused by arotinolol and propranolol were significant (P<0.05) when compared with the corresponding value of the vehicle group (Fig. 2).

Responses to phenylephrine and isoproterenol before and after administration of arotinolol, labetalol and propranolol: Iso-proterenol-induced increases in (+)LVDp/dt were markedly inhibited after administration of arotinolol at both lower and higher doses, labetalol and propranolol by 76±4%, 87±3%, 91±1% and 58±10% of control responses, respectively, while phenylephrine-induced increases in diastolic aortic pressure were significantly inhibited only with labetalol by 52±11% of the control response (Fig. 3).
Table 1. Changes in hemodynamic variables

|                | No stenosis | Before | After drug administration | Recovery |
|----------------|-------------|--------|---------------------------|----------|
|                |             | 2 min  | 15 min                    | 30 min   |
| Vehicle, n=8   |             |        |                           |          |
| MAp (mmHg)     | 109±5       | 104±5  | 105±6                     | 108±5    |
| MCBF (ml/min)  | 34.4±2.5    | 14.1±2.1| 14.3±2.1                  | 14.0±2.1 |
| (+)LVdP/dt (mmHg/sec) | 2243±157 | 1904±116| 1943±123                 | 1950±126 |
| HR (beats/min) | 136±6       | 133±7  | 134±8                     | 135±8    |
| LVEDP (mmHg)   | 3.7±0.4     | 5.8±0.4| 6.1±0.4                   | 5.8±0.3  |
| Arotinolol, 0.05 mg/kg, n=6 |             |        |                           |          |
| MAp (mmHg)     | 118±3       | 113±3  | 113±3                     | 114±3    |
| MCBF (ml/min)  | 27.2±3.6    | 10.0±3.4| 11.0±3.5                  | 11.2±3.4 |
| (+)LVdP/dt (mmHg/sec) | 2492±159 | 1902±115*| 1911±124*                | 1911±137*|
| HR (beats/min) | 134±8       | 122±9**| 119±8**                   | 118±9**  |
| LVEDP (mmHg)   | 3.1±0.5     | 5.1±0.7| 6.3±0.8**                 | 5.8±0.5  |
| Arotinolol, 0.1 mg/kg, n=6 |             |        |                           |          |
| MAp (mmHg)     | 121±2       | 112±4**| 112±4**                   | 112±4**  |
| MCBF (ml/min)  | 32.0±2.0    | 16.2±1.7| 16.0±1.9                  | 16.5±1.9 |
| (+)LVdP/dt (mmHg/sec) | 2721±150 | 2063±112**| 2018±119**               | 2035±124**|
| HR (beats/min) | 148±8       | 127±7**| 123±7**                   | 122±7**  |
| LVEDP (mmHg)   | 3.6±0.3     | 5.2±0.5| 5.8±0.5                   | 5.6±0.6  |
| Labetalol, 1.0 mg/kg, n=6 |             |        |                           |          |
| MAp (mmHg)     | 113±3       | 91±4**  | 100±3**                   | 100±2**  |
| MCBF (ml/min)  | 29.5±3.8    | 9.5±1.8**| 10.3±1.5**                | 10.3±1.5**|
| (+)LVdP/dt (mmHg/sec) | 2455±180 | 1761±129**| 2019±136*               | 2040±147*|
| HR (beats/min) | 160±8       | 149±3*  | 148±4**                   | 149±4*   |
| LVEDP (mmHg)   | 3.0±0.5     | 4.6±0.3| 5.7±0.5**                 | 5.5±0.5*  |
| Propranolol, 0.2 mg/kg, n=6 |             |        |                           |          |
| MAp (mmHg)     | 104±4       | 97±4    | 101±4                     | 102±5    |
| MCBF (ml/min)  | 22.8±3.9    | 9.0±2.5 | 9.7±3.1                   | 10.2±3.3 |
| (+)LVdP/dt (mmHg/sec) | 2023±120 | 1627±83 | 1570±29*                 | 1635±43  |
| HR (beats/min) | 131±8       | 116±8**| 108±5**                   | 108±7**  |
| LVEDP (mmHg)   | 3.4±0.5     | 6.5±1.0*| 6.3±1.0                   | 6.3±0.7  |

MAp=mean aortic pressure, MCBF=mean coronary blood flow, (+)LVdP/dt=peak positive left ventricular dP/dt, HR=heart rate, LVEDP=left ventricular end-diastolic pressure. *P<0.05, **P<0.01, when data during coronary stenosis were compared with those obtained just before drug administration. Data represent the mean±S.E. "Recovery" represents the data obtained 10 min after release of the stenosis.
|                    | No stenosis | Before | After drug administration | Recovery |
|--------------------|-------------|--------|---------------------------|----------|
|                    |             |        | 2 min | 15 min | 30 min |          |
| **Vehicle, n=6**    |             |        |       |        |        |          |
| LAD: EDL (mm)      | 10.7±0.3    | 11.8±0.5 | 11.9±0.5 | 11.8±0.5 | 11.8±0.5 | 10.9±0.5 |
| %SS (%)            | 27.8±3.6    | 31.5±3.7 | 31.7±3.7 | 31.8±3.8 | 31.5±3.9 | 29.0±3.6 |
| LCX: EDL (mm)      | 10.6±0.9    | 12.0±1.0 | 12.1±1.0 | 12.1±1.0 | 12.2±1.0 | 11.1±1.0 |
| %SS (%)            | 15.9±1.4    | 2.1±1.4  | 2.0±1.5  | 2.3±1.4  | 1.8±1.3  | 13.1±1.6 |
| **Arotinolol, 0.05 mg/kg, n=6** |             |        |       |        |        |          |
| LAD: EDL (mm)      | 11.7±0.7    | 12.6±0.6 | 13.1±0.7** | 13.0±0.6* | 12.8±0.6 | 12.3±0.7 |
| %SS (%)            | 23.7±1.4    | 26.8±1.3 | 25.0±1.1* | 25.1±1.0* | 24.8±1.2* | 23.0±1.0 |
| LCX: EDL (mm)      | 12.1±0.6    | 13.6±0.8 | 14.0±0.9** | 14.0±0.8** | 13.8±0.8* | 13.1±0.7 |
| %SS (%)            | 17.5±1.5    | 2.7±0.9  | 4.6±1.1  | 5.0±1.3  | 5.9±1.5  | 14.4±1.7 |
| **Arotinolol, 0.1 mg/kg, n=6** |             |        |       |        |        |          |
| LAD: EDL (mm)      | 12.0±0.7    | 12.7±0.8 | 13.0±0.9 | 13.0±1.0 | 13.0±1.1 | 12.7±1.0 |
| %SS (%)            | 21.9±2.2    | 26.2±2.2 | 23.9±2.2 | 23.0±2.6** | 22.5±2.2** | 21.5±2.3 |
| LCX: EDL (mm)      | 12.0±1.4    | 13.2±1.5 | 13.5±1.6 | 13.5±1.6 | 13.4±1.5 | 13.1±1.5 |
| %SS (%)            | 16.1±1.2    | 2.3±1.3  | 4.7±0.7  | 5.9±0.8** | 6.5±1.2** | 10.5±1.1 |
| **Labetalol, 1.0 mg/kg, n=6** |             |        |       |        |        |          |
| LAD: EDL (mm)      | 12.0±0.3    | 13.2±0.4 | 13.9±0.5** | 13.7±0.5** | 13.5±0.5 | 12.8±0.6 |
| %SS (%)            | 20.9±2.7    | 29.1±2.4 | 27.1±1.4 | 27.6±1.5 | 27.9±1.4 | 26.0±1.8 |
| LCX: EDL (mm)      | 10.0±1.1    | 11.2±1.1 | 11.9±1.2** | 11.7±1.2** | 11.6±1.2** | 10.7±1.1 |
| %SS (%)            | 14.0±1.2    | 3.0±0.9  | 2.0±0.7  | 3.8±1.8  | 4.8±1.7  | 12.9±1.8 |
| **Propranolol, 0.2 mg/kg, n=6** |             |        |       |        |        |          |
| LAD: EDL (mm)      | 10.6±1.0    | 11.4±1.1 | 11.9±1.2* | 11.8±1.2  | 11.6±1.2 | 11.3±1.2 |
| %SS (%)            | 25.4±3.6    | 30.1±4.1 | 28.5±4.0 | 27.0±3.6* | 26.9±3.3* | 25.6±3.5 |
| LCX: EDL (mm)      | 10.7±1.3    | 11.9±1.3 | 12.2±1.3* | 12.1±1.3  | 12.0±1.3 | 11.5±1.2 |
| %SS (%)            | 14.8±1.1    | 2.3±1.9  | 4.6±1.6  | 7.9±2.3** | 8.9±2.8** | 12.3±1.7 |

LAD=left anterior descending coronary artery-perfused (non-ischemic) area, LCX=left circumflex coronary artery-perfused (ischemic) area, EDL=end-diastolic length, %SS=percent segment shortening. *P<0.05, **P<0.01, when data during coronary stenosis were compared with those obtained just before drug administration. Data represent the mean±S.E. "Recovery" represents the data obtained 10 min after the release of the stenosis.
Fig. 1. Original tracing from one dog receiving arotinolol at 0.05 mg/kg, i.v., in the presence of stenosis of the left circumflex coronary artery (LCX). AoP=aortic pressure, CBF=blood flow of the LCX, MCBF=mean blood flow of the LCX, LVP=left ventricular pressure, LVdP/dt=first derivative of LVP, LAD=left anterior descending coronary artery-perfused (non-ischemic) area, LCX=LCX-perfused (ischemic) area, HR=heart rate. The time between the recordings obtained before coronary stenosis and the drug injection was around 30 min. "RECOVERY" represents recordings obtained 10 min after release of the stenosis.

Discussion

Data obtained with the vehicle group clearly demonstrated the stability of the present experimental model up to at least 30 min after the administration, since no significant alteration in hemodynamic and contractility parameters was seen during that period as compared to the predrug value. Thus, modifications in all parameters after drug administration were regarded to result from its pharmacological effects.

We found that arotinolol improved regional dysfunction distal to a coronary stenosis associated with apparent decreases in heart rate and (+)LVdP/dt, which were qualitatively similar with those seen with propranolol. Previous investigations have consistently shown that propranolol exerts beneficial influences on the ischemic myocardium in dogs with coronary stenosis, as evidenced by favorable redistribution of myocardial blood flow (12-14) and/or improvement of regional function (9, 13-16) or restoration of myocardial pH (17). The present results with propranolol are also in accord with these studies. According to Vatner (18) and Gross et al. (14), endocardial perfusion in the ischemic area has been demonstrated to correlate with regional myocardial function. In this context, it is reasonable that improvement of regional shortening seen after arotinolol as well as propranolol in our experiments can be considered as alleviation of myocardial ischemia, although regional myocardial blood flow distribution was not measured. As generally
accepted, beta-adrenoceptor blockers improve the imbalance between oxygen-supply and demand of the ischemic heart mainly through their negative inotropic and brady-cardiac actions which elicit the reduction of myocardial oxygen consumption and in addition, the increase of oxygen supply by prolongation of diastolic perfusion time. Arotinolol exerted the negative inotropic and chronotropic actions associated with marked inhibition of isoproterenol-induced responses. Thus, by analogy with propranolol, the beneficial effect of arotinolol on segment shortening in the region of the ischemic myocardium appears to be attributable primarily to its beta-blocking actions.

Fig. 2. Changes in heart rate (HR), peak positive left ventricular dP/dt (\(+\)LVdP/dt), the product of HR and systolic aortic pressure (sAoP) and percent segment shortening (%SS) in ischemic (LCX) zone from the respective predrug value after administration of saline (open circles, n=8); arotinolol, 0.05 mg/kg (closed circles, n=6); labetalol, 1.0 mg/kg (open squares, n=6); and propranolol, 0.2 mg/kg (closed squares, n=6). *P<0.05 when compared with the respective predrug value. Data represent the mean with lines showing S.E.
Labetalol (1.0 mg/kg) at the dose employed in the present experiments produced the most potent inhibition of isoproterenol-induced responses as compared to arotinolol or propranolol and caused significant decreases in both heart rate and (+) LVdP/dt and further, caused a relatively large reduction in rate-pressure product, which is conventionally used as an index of myocardial oxygen consumption. Nevertheless, this agent failed to improve impaired regional function during coronary stenosis in contrast to arotinolol or propranolol. In preliminary experiments (n=4), no favorable change in myocardial regional function in the ischemic region was also observed with 0.5 mg/kg of labetalol. Major differences in pharmacological properties of labetalol from those of propranolol or arotinolol appear to result from the alpha-adrenoceptor blocking action as shown by the observation that only labetalol significantly inhibited phenylephrine-induced responses (Fig. 3). The potency of the alpha-blocking effect of arotinolol is reported to be only one fourth to one fifth that of labetalol (1, 2, 5).

Takegoshi et al. (19) have demonstrated that...
the relative potencies of alpha- and beta-blocking effects of arotinolol are 1:8, whereas those of labetalol are approximately 1:3 (20). It is possible that the relative potencies of alpha- and beta-blocking effects of drugs might be profoundly related to the different efficacy of these three drugs on myocardial ischemia.

Theoretically, blockade of the alpha-adrenoceptors leads to the systemic vasodilatation which will produce dual effects in the ischemic heart. The beneficial aspects of these dual effects are that, first, myocardial oxygen consumption would be reduced by decreases in afterload and preload to the heart due respectively to vasodilatation of resistance and capacitance vessels; second, the rises in left ventricular volume and coronary vascular resistance which are commonly observed after beta-blockade would be lessened to some extent; and third, the coronary arterial spasm might be prevented partly by dilatation of the large proximal coronary arteries which have a greater amount of alpha-adrenoceptor activity than the small distal ones (21). On the other hand, hypotension caused by the systemic vasodilatation will lower coronary perfusion pressure and thereby compromise blood-supply to the myocardium distal to the severe coronary narrowing due to loss of autoregulation (22). Hypotension would also induce the reflex-mediated sympathetic stimulation. This might counteract the negative inotropic and chronotropic action due to the beta-adrenoceptor blockade to some extent. Although several clinical studies (23–26) show that alpha-adrenoceptor blockade improved a capability to exercise in some patients with angina pectoris, reduction of the systemic vascular resistance produced by alpha-blockade may be detrimental to other patients with fixed stenosis because of the large pressure drop that occurs across a coronary stenosis (27). Thus, the reason why labetalol did not improve the ischemic segment shortening in our experimental model with fixed stenosis may be mainly attributable to the relatively large decline in aortic pressure which further reduced the limited coronary blood flow in the presence of a stenosis. Additionally, Berdeaux et al. (28) demonstrated that labetalol did not induce the favorable redistribution of myocardial flow during acute coronary occlusion in dogs, and they suggested that one of the major requirements for the development of coronary blood flow redistribution phenomena induced by beta-adrenoceptor blocking agents is the unmasking of the alpha-adrenoceptor-mediated coronary vasoconstrictor tone. This implies that alpha-blockade would abolish the redistribution phenomenon as shown in the previous study (29).

However, the merits and demerits of these possible hemodynamic changes caused by alpha-blockade concomitantly with beta-blockade in the treatment of myocardial ischemia appear to vary largely depending on the experimental model employed or the individual case of patients with coronary artery disease. Unfortunately, the effect of combined alpha- and beta-adrenoceptor blockers on myocardial ischemia, especially that induced by coronary spasm, remains to be investigated.

In conclusion, the present results obtained with the anesthetized dogs demonstrate that arotinolol, distinct from labetalol, improves impairment of regional myocardial function distal to a coronary stenosis in a similar manner to propranolol.

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