Acta Medica Okayama

Volume 42, *Issue* 6 1988 *Article* 5

DECEMBER 1988

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Abstract

The effect of the heart rate and myocardial contractile force on the extravascular resistance to blood flow of the left anterior descending coronary artery (LAD) was evaluated in 15 mongrel dogs anesthetized with sodium pentobarbital. The LAD was maximally dilated by intracoronary infusion of adenosine, which precluded the influence of vasomotor tone. Increases in the heart rate and myocardial contractile force decreased coronary blood flow in the absence of a change in coronary perfusion pressure. The changes in mean coronary resistance showed a significant linear relationship to changes in developed tension. The changes in coronary resistance caused by varying the heart rate and contractile force were so small that a normal coronary vascular tree could easily compensate for the increase in resistance. However, it is supposed that with critical stenosis of the vascular tree even a small increase in resistance might cause deleterious effects on coronary blood flow.

KEYWORDS: contractile force, tachycardia, extravascular resistance, coronary flow, adenosine

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*PMID: 3239438 [PubMed - indexed for MEDLINE]

Acta Med Okayama 42 (6) 335-342(1988)

Effect of Heart Rate and Myocardial Contractile Force on Coronary Resistance

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The effect of the heart rate and myocardial contractile force on the extravascular resistance to blood flow of the left anterior descending coronary artery (LAD) was evaluated in 15 mongrel dogs anesthetized with sodium pentobarbital. The LAD was maximally dilated by intracoronary infusion of adenosine, which precluded the influence of vasomotor tone. Increases in the heart rate and myocardial contractile force decreased coronary blood flow in the absence of a change in coronary perfusion pressure. The changes in mean coronary resistance showed a significant linear relationship to changes in developed tension. The changes in coronary resistance caused by varying the heart rate and contractile force were so small that a normal coronary vascular tree could easily compensate for the increase in resistance. However, it is supposed that with critical stenosis of the vascular tree even a small increase in resistance might cause deleterious effects on coronary blood flow.

Key words : contractile force, tachycardia, extravascular resistance, coronary flow, adenosine

Systolic contraction produces compression of the coronary vessels increasing their resistance to blood flow(1, 2). Lewis and coworkers (3) have shown that coronary blood flow increases after the induction of ventricular asystole or ventricular fibrillation, when the heart is perfused at a constant pressure. The extravascular compression is highest in the subendocardium (4, 5) and thought to be responsible for the vulnerability of the subendocardium to injury in ischemic heart disease (6). Though these investigations have indicated that extravascular resistance is far from negligible, few reports are concerned with the effects of the myocardial contractility state and of the relative changes in the heart rate on coronary blood flow.

The present study attempts to correlate changes in myocardial force and in heart rate with changes in coronary blood flow in the heart with the coronary arteries maximally dilated. This approach allows quantitatively the documentation of the effects of changes in extravascular compression on

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the overall coronary resistance with or without autoregulatory function of blood flow.

Materials and Methods

Surgical preparation. The study was performed on fifteen healthy mongrel dogs of both sexes weighing 12-17 kg. The dogs were anesthetized with an intravenous injection of sodium pentobarbital, 25 mg/kg, and ventilated with O_2-enriched air by means of a positive-pressure respirator attached to an endotracheal tube. Arterial PO_2, PCO_2 and pH were determined every 30 min (Corning Model 165-II) and maintained in the ranges of PO_2, 80-120 mmHg, PCO_2, 35-45 mmHg and pH, 7.34-7.45. A left thoracotomy was performed, the pericardium was opened, and the heart was cradled in the pericardial sac. An electromagnetic flow probe and plastic occlusive snare were positioned around the left anterior descending coronary artery (LAD) near its origin. A plastic catheter was inserted transmurally into the coronary lumen distal to the snare. A Y-connector linked this coronary catheter to two infusion syringes, permitting the simultaneous administration of two solutions at different rates. Catheters introduced into the aortic root via the right femoral artery and into the left ventricle via the left common carotid artery were used to measure coronary perfusion pressure and left ventricular pressure, respectively. Regional myocardial force was measured using a strain gauge arch (modified Model TH-602T, Nihon-Koden Company, Tokyo, Japan). We already reported that this strain gauge arch is sensitive to changes in contractility but not to changes in preload or afterload (7). This gauge was held against the left ventricular anterior wall perfused by the LAD and fixed perpendicular to the base-apex axis of the heart with transmural needles. The gauge stretched the muscle segment between the needles to approximately 130% of the initial length. To compensate for a significant variation of resting tension due to the needle insertion in different phases of a cardiac cycle, we assumed the force recorded at the end of diastole before adenosine infusion as zero tension. Pacing electrodes were sutured onto the right atrial appendage. The surgical preparations are schematically represented in Fig. 1. Aortic and left ventricular pressures, coronary blood flow and local myocardial force were recorded continuously on a Jet Recorder (Model NJ-13BL, Nihon-Koden Company) at paper speeds of 2.5 mm/sec and 50 mm/sec.

Adenosine (Sigma Chemical Company, St Louis, MO, USA) and isoproterenol (Nikken-Kagaku

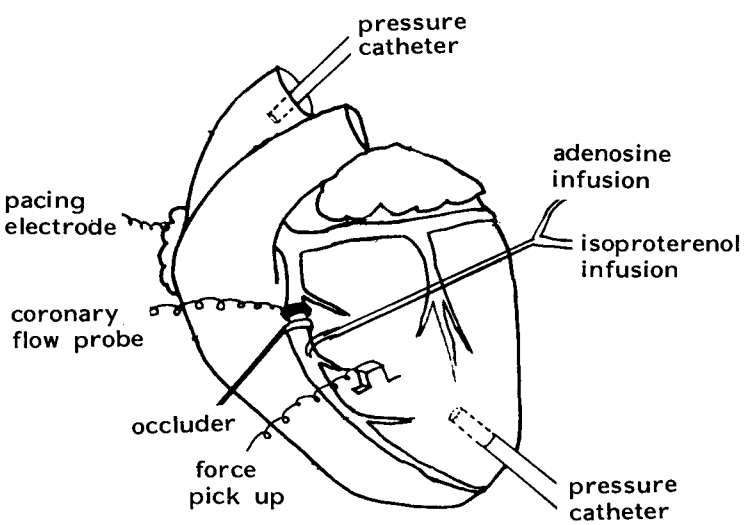

Fig. 1 Schematic illustration of instrumentations.

Co. Ltd., Tokyo, Japan) were dissolved in physiological saline just prior to use at concentrations of 1 mM and 9.47 μM, respectively.

Experimental protocol. All experiments were performed during maximal dilatation induced by intracoronary infusion of 1 mM adenosine into the LAD at a rate of 1.5 ml/min. The following two methods were used to verify the maximal dilatation: 1) doubling of the adenosine dose, and 2) occlusion of the coronary branch for 30 sec and observation of reactive hyperemia.

The effect of heart rate on extravascular compression of the coronary beds was tested in the first group of 6 dogs. After recording the control values, adenosine was infused into the coronary artery. Then, the sinus node was crushed mechanically, and sinus bradycardia with a heart rate of less than 130 beats/min was achieved. After that, the heart was paced at a rate of 150 beats/min with the continuous infusion of adenosine. After hemodynamic steady state was achieved, the pacing rate was increased to 180 or 210 beats/

Table 1 Effect of the heart rate (HR) on blood pressure (BP), left ventricular end-diastolic pressure (LVEDP), coronary blood flow (CBF), developed tension (dT) and coronary resistance (CR)[a]

Intervention	HR (beat/min)	BP (mmHg)	LVEDP (mmHg)	CBF (ml/min/100 g)	dT (g/mm²)	CR (mmHg/ml/min/100 g)
Control	158 ± 1	108 ± 5	6.8 ±1.6	77.3** ± 7.9	47 ± 7	1.406** ±0.150
Ado alone[b]	158 ± 10	106 ± 6	6.6 ±1.6	452.7 ± 76.0	47 ± 7	0.249 ±0.048
Pacing 150	150	106 ± 6	6.9 ±2.0	456.2 ± 71.1	47 ± 7	0.241 ±0.048
Pacing 180	180	106 ± 4	6.8 ±1.8	434.8* ± 79.1	47* ± 7	0.248* ±0.048
Pacing 210	210	106 ± 5	7.1 ±2.2	434.8* ± 86.1	41* ± 8	0.255* ±0.056

a: The data are expressed as the mean ± SD. Asterisks indicate significant differences from the values at a pacing rate of 150/min: *, $p < 0.05$ and **, $p < 0.01$

b: Ado alone means infusion of adenosine alone (1 mM, 1.5 ml/min). Pacing was carried out during adenosine infusion.

Table 2 Effect of isoproterenol (ISP) on the heart rate (HR), blood pressure (BP), left ventricular end-diastolic pressure (LVEDP), coronary blood flow (CBF), developed tension (dT) and coronary resistance (CR)[a]

Intervention	HR (beat/min)	BP (mmHg)	LVEDP (mmHg)	CBF (ml/min/100 g)	dT (g/mm²)	CR (mmHg/ml/min/100 g)
Control	162 ± 19	110 ± 13	6.9 ±1.7	77.8** ± 11.2	46 ± 9	1.069** ±0.426
Ado alone	160 ± 16	107 ± 13	6.8 ±1.8	490.4 ±104.8	43 ± 7	0.224 ±0.032
ISP 83.3	164 ± 16	107 ± 14	5.8* ±1.4	457.8* ±101.7	74** ±13	0.241** ±0.035
ISP 333	169 ± 14	107 ± 14	5.4* ±1.6	400.1** ± 92.0	98** ±13	0.274** ±0.038
Ado after	160 ± 17	105 ± 10	7.1 ±2.1	473.9 ± 91.3	46 ± 6	0.227 ±0.034

a: The data are expressed as the mean ± SD. Asterisks indicate significant differences from the values of Ado alone: *, $p < 0.05$ and **, $p < 0.01$. Ado alone, infusion of adenosine alone (1 mM, 1.5 ml/min) before isoproterenol; ISP 83.3 and ISP 333, during infusion of isoproterenol at a rate of 83.3 μl/min and of 333 μl/min, respectively, with adenosine infusion; Ado after, infusion of adenosine alone after termination of isoproterenol infusion.

min, and then returned to 150 beats/min.

In the second group of a dog, the influence of increases in myocardial contractility on calculated coronary resistance was examined using intracoronary infusion of isoproterenol. One mM adenosine was infused into the coronary artery from one syringe at a rate of 1.5 ml/min, and physiological saline was infused from the other at a rate of 200 μl/min. Three minutes later, physiological saline was switched to 2 μg/ml (9.47 μM) of isoproterenol solution. Isoproterenol infusion began at a rate of 83.3 μl/min (166.6 μg/min), and 3 min later the rate was increased to 333 μl/min (666 μg/min). After 3 more min, isoproterenol solution was switched to physiological saline again, and post-control data were obtained.

Data analysis. For evaluating the effects of extravascular support on resistance to flow, we calculated mean coronary resistance as the mean aortic blood pressure (coronary perfusion pressure) divided by the mean coronary blood flow. Analysis of variance employing Bonferroni's t-test of significance was used to examine the null hypothesis that heart rate change or isoproterenol would not alter the vascular resistance of the LAD. Differences were considered significant at the level of $p < 0.05$. Data are expressed as the mean $\pm$ SD.

Results

Results are summarized in Tables 1 and 2. The baseline vascular resistance of the LAD was 1.41 ± 0.15 mmHg/ml/min per 100 g in the cardiac pacing group, and 1.07 ± 0.43 mmHg/ml/min per 100 g in the isoproterenol group. Before crushing the sinus node, the dose of adenosine did not alter the heart rate, coronary perfusion pressure or left ventricular end-diastolic pressure (LVEDP), but decreased coronary resistance to about 20% of the value before adenosine and increased coronary blood flow about 6 times. Developed tension of local myocardial force was not affected by intracoronary infusion of adenosine. Attainment of maximal coronary vasodilation by adenosine infusion was confirmed by the findings that doubling of the adenosine dose did not cause a further increase in coronary blood flow, and that reactive hyperemia was not observed following a 30-second coronary occlusion.

Changes in the heart rate. Resistance of the LAD during right atrial pacing at a rate of 150 beats/min was not significantly different from the resistance during sinus rhythm in the presence of adenosine. Changes in the pacing rate did not affect aortic blood pressure or LVEDP. The coronary resistance increased slightly but significantly with stepwise augmentation of the pacing rate from 150 beats/min to 180 and 210 beats/min. An increase in the pacing rate reduced developed tension slightly but increased resting tension slightly. However, changes in coronary resistance did not show a significant relationship to the heart rate, resting tension or developed tension.

Changes in contractile force. Intracoronary infusion of isoproterenol in the presence of a large dose of adenosine (1.5×10^{-6} mol/min) did not modify aortic blood pressure, but slightly increased the heart rate. The calculated intracoronary concentrations of isoproterenol were 0.364 μg/ml at an infusion rate of 83.8 μl/min and 1.661 μg/ml at a rate of 333 μl/min. Isoproterenol lowered LVEDP slightly but significantly. Coronary resistance increased with isoproterenol infusion in a dose dependent manner; 166.6 μg/min and 666 μg/min of isoproterenol increased the resistance by $6.6 \pm 3.08\%$ and $17.9 \pm 4.99\%$, respectively. The developed tension of local myocardial force increased in parallel with a rise in the isoproterenol infusion rate. Isoproterenol injected at a rate of 166.6 μg/min also increased the resting tension significantly, but no further increases in the resting tension were observed by an increase in the infusion rate to 666 μg/min. Fig. 2 shows the relationship of changes in coronary resist-

ance to changes in developed tension. Linear regression analysis revealed a significant relationship ($r = 0.76$, $p < 0.01$) between the two indices, which was indicated by the following formula when developed tension was in the range of 10-80 g/mm^2: Δcoronary resistance $= 86.7 \times 10^{-5}$ (Δdeveloped tension) $- 84.2 \times 10^{-4}$, where Δcoronary resistance is the change in the resistance, and Δdeveloped tension is the change in the tension from the developed tension during the infusion of adenosine alone. Neither resting tension nor LVEDP showed a significant relationship to coronary resistance.

Twenty minutes after termination of isoproterenol infusion, all hemodynamic parameters measured returned to the levels before isoproterenol infusion.

Discussion

Coronary blood flow depends on the coronary driving pressure and on the resistance to flow in the coronary arteries. The coronary vascular resistance is changed by altering the tone of the coronary arteries and extravascular support. The present studies were conducted during maximal pharmacological vasodilation of the coronary artery which precluded changes in vasomotor tone. In addition, coronary blood flow exceeded any possible metabolic requirements of the myocardium, since the flow during coronary infusion of adenosine reached to the level as much as possible. Thus, metabolic and vasomotor effects did not influence the results. The coronary driving pressure was almost constant in the present study as indicated by the constant aortic pressure. Therefore, it can be concluded that during maximal dilatation alterations in coronary resistance are caused by changes in the extravascular support. Sabbah *et al.* (8) found a significant relationship between changes in epicardial intramyocardial pressure and

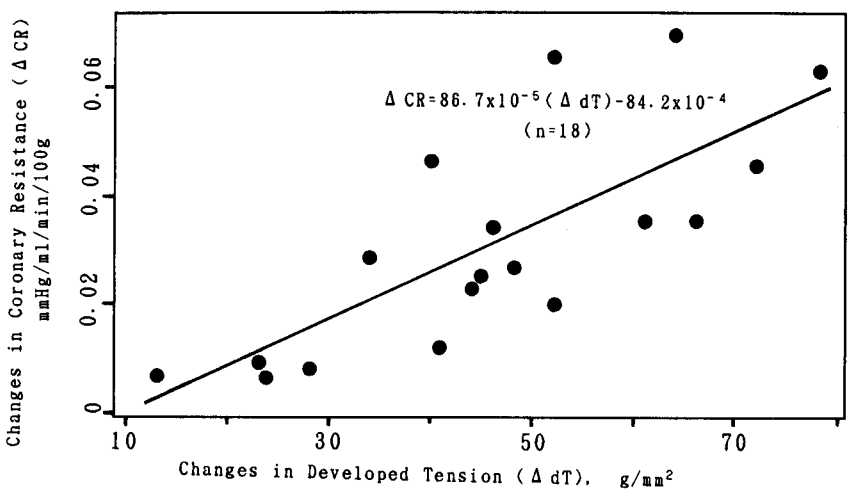

Fig. 2 Relationship of changes between coronary resistance and developed tension. When the developed tension was in the range of 10-80 g/mm^2, there was a significant linear relationship ($r = 0.76$, $p < 0.01$) between two parameters, represented by the following formula; Δ coronary resistance $= 86.7 \times 10^{-5}$ (Δ developed tension) $- 84.2 \times 10^{-4}$. Δ coronary resistance, changes in the resistance from values during infusion of adenosine alone. Δ developed tension, changes in the tension from values during infusion of adenosine alone.

changes in coronary resistance in the dog. Subendocardial myocardial blood flow and the endo/epi flow ratio decreased with an increase in myocardial contractility, and L'Abbate and his associates (9) suggested a waterfall mechanism from findings of higher zero flow intercept of pressure-flow relationship in the endocardial myocardial layer. Downey *et al.* (10) demonstrated, using ejecting and isovolumetrically contracting hearts that cardiac strain associated with shortening of the myocardium affected extravascular support of coronary resistance to a small extent, while compressive stresses in the myocardium associated with pressure development had a large effect on extravascular support.

We utilized the regional contractile force measured with a strain gauge arch as an index of extravascular support instead of measurements of left ventricular dP/dt, because the latter measurements carried out by previous authors (1, 3, 11) were much less sensitive to local changes in myocardial contractility when isoproterenol was directly infused into the LAD. Though changes in both preload and afterload are known to affect dP/dt and contractile force, the gauge used here is rather insensitive to changes produced by preload and afterload (7). Therefore, it is reasonable to consider that results measured with our gauge essentially represented the myocardial force alone.

Increasing the heart rate by changing the rate of electrical stimulation shortened diastole with a relative increase in systole in a heart cycle and slightly decreased developed tension of the local myocardial force. An increase in coronary resistance was observed whenever the heart rate was increased. Since the aortic blood pressure was found constant at rates of 150-210 beats/min, the increase in resistance is attributed to an increase in the extravascular support, though changes in resistance did not significantly correlate with the indices of myocardial contraction or intraventricular pressure. However, the increase in the resistance was quite small in magnitude. Only a 5.9% increase in coronary resistance was observed when the heart rate increased from 150 to 210 beats/min. This increase in resistance per beat was 0.10% of the index at a rate of 150 beats/min. Our results are consistent with those of Sabiston and Gregg (1), Lewis *et al.* (3), and Raff *et al.* (11). Hirche and his associates (12) reported that heart rate did not influence extravascular support. The discrepancy may be accounted by the wide variation in resistance between different dogs. According to Raff *et al.* (11), coronary resistance increased by 0.037 mmHg/ml/min per 100 g when the heart rate was increased by 100 beats/min. This value is small enough to be shielded by differences in experimental design if the heart rate is varied in a relatively narrow range.

Isoproterenol infused into the LAD during maximal vasodilation increased myocardial contractility, which was manifested by a significant increase in developed tension of the local myocardium. Sabban *et al.* (8) reported that an intracoronary injection of 1 μg isoproterenol significantly increased subepicardial intramyocardial pressure from 127 to 204 mmHg (about a 61% increase), exceeding systolic aortic pressure. The maximum concentration of isoproterenol calculated from their data was similar to the concentration used in this study, if one can assume that in their study coronary blood flow during adenosine administration was the same as in ours. This observation suggests that the isoproterenol used in the present study possibly caused an increase in intramyocardial pressure similar to the increase described by Sabbah *et al.* In the present study, intracoronary infusion of isoproterenol caused a substantial increase in the

coronary resistance in a dose-dependent manner. A close relationship was observed between changes in the coronary resistance and changes in myocardial developed tension. Furthermore, isoproterenol affected extravascular support much more than atrial pacing. Intracoronary-administered isoproterenol increased the heart rate significantly. However, isoproterenol at an infusion rate of 666 μg/min increased the heart rate by only 10 beats/min on the average. This increase in the heart rate corresponds roughly to an increase in the resistance of 0.0025 mmHg/ml/min per 100 g (1.1% before isoproterenol), whereas the total increase in the resistance was by 0.05 mmHg/ml/min per 100 g (Table 2). Thus, the contribution of the heart rate change to the increase in the resistance during isoproterenol infusion was negligible. Marzilli *et al.* (13) and L'Abbate and coworkers (9) observed that during isoproterenol infusion, myocardial blood flow decreased and flow to the inner and outer layers of the myocardium was shown to be related inversely to changes in local myocardial motion. They concluded that the changes in extravascular resistance could result in wide fluctuations in coronary flow, and that localized contractile performance is the major contributing factor to coronary vascular resistance. The present results are consistent with theirs.

Quantitative evaluation of the changes in extravascular support due to alterations in the heart rate and myocardial contractile force leads to the conclusion that the contractile force has a greater contribution than the heart rate. An increase in the heart rate increases the resistance only 0.10% per beat. A change in myocardial contractile force of 1 g/mm^2 leads to a 0.000867 mmHg/ml/min per 100 g change in coronary flow resistance. These results indicate that a normal coronary vascular tree easily compensates for an increase in resistance, since an increase in extravascular support by both the heart rate and myocardial contractile force affects coronary resistance only to a small extent. However, even a small increase in resistance caused by an increase in extravascular support might have deleterious effects on coronary blood flow if the vascular tree was stenotic, because a vascular bed with a critical stenosis does not have the vasodilatory capacity in response to vasodilatory stimuli.

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Reccived July 13, 1988; accepted October 11, 1988