Effects of Nipradilol, a New β-Adrenoceptor Blocking Agent with Vasodilating Properties, on Transmural Energy Metabolism in the Underperfused Canine Heart

Makie HIGUCHI and Takeo ASAKAWA
Department of Pharmacology, Saga Medical School, Saga 840-01, Japan
Accepted February 20, 1987

Abstract—Effects of nipradilol on hemodynamics and transmural energy metabolism of underperfused (ischemic) canine hearts were investigated. The ischemic heart was prepared by constricting a tube connecting the circumflex coronary artery with the carotid artery for 10 min so that the perfusion pressure (CPP) was reduced to 30 mmHg. The reduction in CPP resulted in decreases in coronary blood flow (CBF) by 70%, regional myocardial contractile force (MCF) by 30%, myocardial ATP contents by 32% (inner layer)—22% (outer) and creatine phosphate by 75% (inner)—60% (outer). Increases in the left ventricular end diastolic pressure (LVEDP) by 4.8 mmHg, myocardial inorganic phosphate contents by 1.9 times (inner)—1.3 (outer) and lactate by 4.3 times (inner)—2.4 (outer) were also observed. In dogs with normal hearts, an infusion of nipradilol (10 μg/kg/min, i.v., for 15 min) decreased CPP by 25%, CBF by 40%, cardiac effort index by 45% and MCF by 30 to 40%, and it slightly increased LVEDP without affecting myocardial high-energy phosphate and lactate levels. In ischemic hearts, nipradilol infusion starting 5 min before ischemia attenuated the ischemia-induced elevation of LVEDP to 1.8 mmHg, and the ischemia-induced changes in high-energy phosphate contents to 1/2 (inner)—1/3 (outer) and changes in lactate to 1/6 (inner)—1/10 (outer). These results indicate that nipradilol improves the ischemic derangement of both transmural energy metabolism and hemodynamics.

Nipradilol is a newly developed anti-hypertensive agent which possesses both β-adrenoceptor blocking and vasodilating properties (1). It has been shown that the vasodilating properties are probably due to α-adrenoceptor blocking action, especially α1-blocking action (2—4), and nitroglycerin-like action (5, 6). In spontaneously hypertensive rats, nipradilol produces a long-lasting antihypertensive effect (7). Hypertension is a risk factor for ischemic heart disease, and the clinical significance of β-adrenoceptor blocking agents and nitroglycerin-like vasodilators has been well established for treatment of ischemic heart disease. In previous reports (8, 9), both β-adrenoceptor blocking and nitroglycerin-like agents were shown to improve the ischemic derangement of the myocardial energy metabolism. Therefore, it is expected that nipradilol also has a beneficial effect on the myocardial function and energy metabolism of ischemic hearts.

In the present experiment, the effects of nipradilol on hemodynamics, especially myocardial contractile function and left ventricular end diastolic pressure (LVEDP), and on transmural distribution of high-energy phosphates (ATP, CP) and lactate in the myocardium were investigated in pentobarbital-anesthetized open-chest dogs, in which coronary perfusion pressure (CPP) was reduced to 30 mmHg by acute coronary stenosis. To obtain reliable effects, nipradilol was infused intravenously at 10 μg/kg/min for 15 min. Referring to the results in anesthetized dogs (1, 7), it has been shown that the minimal effective doses of nipradilol for
decreasing heart rate (HR) and mean systemic blood pressure (SP) are 1 μg/kg, i.v., and 10 μg/kg, i.v., respectively; and the single i.v. administration of 100 μg/kg causes approximately 20% decreases in both HR and SP and a reduction in LVEDP.

Materials and Methods

Experiments were performed on 25 mongrel male dogs weighing 11.9 (10.5–14.0) kg. The experimental procedures used are essentially the same as those described in the previous publications (9–11). Dogs were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and artificially ventilated through a cuff-type endotracheal tube with a mixture of room air and oxygen to maintain arterial oxygen tension within the normal range. A left thoracotomy was performed through the fifth intercostal space, and the heart was supported in the pericardial cradle. The proximal portion of the left circumflex coronary artery (LC) was dissected free from the surrounding connective tissue, and a glass cannula attached to a polyethylene tube was inserted into the coronary artery after heparinization (500 U/kg, i.v., initially; an additional 1,000 U every 30 min). The area supplied by the LC (LC-area) was perfused with the animal’s own blood led from the left common carotid artery through an extra-corporeal circuit. Myocardial tension developments described as myocardial contractile force (MCF) were measured using two isometric strain-gauge arches (Nihon Kohden, Tokyo, Japan; model TH-601 T), which were attached to the epicardium in parallel with the longitudinal axis of the subepicardial muscle. The myocardial segment under the 2 feet of each strain-gauge arch was stretched by 25–30 percent of its initial diastolic length. One arch was sewn to the epicardium in the LC-area (underperfused area), and the other in the area supplied by the left anterior descending coronary artery (LAD) (LAD-area: normally perfused area). Other parameters were obtained as follows: mean CPP via a side tube of the circuit using an electronic manometer (Nihon Kohden, model MPU-0.5), mean coronary blood inflow (CBF) by an electromagnetic flow meter (Nihon Kohden, model MFV-2100) interposed in the circuit, intraventricular pressure via a polyethylene tube inserted into the left ventricular cavity through the left atrial appendage, SP through a cannula inserted into the femoral artery, and HR with a cardiotachometer (Nihon Kohden, model AT-600G). All parameters were recorded continuously (Nihon Kohden, model RM 6000). After completion of these surgical procedures, the animals were allowed to recover for 30 to 60 min. Then CPP was altered by constricting the tube of the extracorporeal circuit with a screw clamp placed before the measuring points of CPP and CBF.

The animals were divided into four groups; the experimental protocol is shown in Fig. 1. In Group I (control group, six dogs) and Group III (six dogs), physiological saline (solvent) was administered via the saphenous vein for 15 min at an infusion velocity of 2 ml/min using a syringe pump (Truth, model A II). In Group II (seven dogs) and Group IV (six dogs), nispradilol (10 μg/kg/min) was infused in the same manner. In Group III and Group IV, 5 min after the infusion of agents, CPP was decreased to 30 mmHg for 10 min. Except when the agents were perfused, electrolytic solution (Shimizu, SOLITA-T No. 3) was administered continuously at an infusion velocity of about 20 ml/hr. Ionic composition in the solution was as follows: Na+, 35; K+, 20; Cl−, 35; lactate, 20 (mEq/L); and glucose, 43 (g/L).

Myocardial biopsies of the LC-area were obtained 15 min after the infusion of the agents using an electrical drill with a cork borer. The myocardial tissue (200–300 mg) was freeze-stopped between aluminum blocks precooled in liquid nitrogen. Sampling time was approximately 5 sec. The specimen was dissected into an inner, middle and outer third, corresponding, respectively, to the subendocardial, midcardial and subepicardial portions of the left ventricle. The solidly frozen tissue was weighed (wet weight). After the tissue was lyophilized for 5 hr, the tissue was weighed again (dry weight). Then, the tissue was pulverized and extracted by 0.6 M perchloric acid. The mixture was centrifuged at 10,000 rpm for 15 min at 2°C. The supernatant was used for determination of ATP, creatine phosphate (CP), inorganic phosphate (Pi) and lactate. The method of...
Fig. 1. Experimental protocol. Physiological saline infusion for Group I and III and nipradilol infusion at 10 μg/kg/min for Group II and IV, all at the velocity of 2 ml/min into the saphenous vein (i.v.), were administered for 15 min. All injections were by a syringe pump. In Group III and IV, 5 min after the infusion of agents, coronary perfusion pressure (CPP) was decreased to 30 mmHg by partial constriction of the extracorporeal circuit tube for 10 min. Myocardial biopsies were obtained following 15-min infusions.

Statistical analysis was carried out using Student’s t-test.

Results

Effects of nipradilol on hemodynamics under normal coronary perfusion: Changes in hemodynamic function caused by agents under normal coronary perfusion are summarized in Figs. 2–8. No changes were observed in the parameters after the administration of 0.9% NaCl, 2 ml/min, i.v., for 15 min (Group I, control group).

Intravenous infusion of nipradilol, 10 μg/kg/min, (Group II) caused gradual decreases in CPP, SP, left ventricular peak systolic pressure (LVPP) and HR; and 15 min after the infusion, the levels stabilized to a constant low level, approximately 25% lower than the control (Figs. 2 and 8). The cardiac effort index (mean SP×HR) and CBF also decreased gradually by approximately 45% and 40% of the control, respectively (Figs. 7 and 3). After nipradilol infusion, LVEDP showed a slight but significant elevation (+0.9±0.3 mmHg) (Fig. 6). MCF decreased in both areas; and 5 min after the infusion, it stayed at an almost constant low level, 30–40% lower than the control (Figs. 4 and 5).

Effects of partial coronary constriction with and without nipradilol on hemodynamics: Changes in hemodynamic function caused by acute coronary stenosis, at a CPP of 30 mmHg for 10 min, in the absence or presence of nipradilol are summarized in Figs. 2–8. Partial coronary constriction under 0.9% NaCl infusion (Group III) caused decreases of approximately 70% and 30%, respectively, in CBF and MCF in the underperfused area (LC-area) (Figs. 3 and 4), and it caused marked elevation in LVEDP (+4.8±0.9 mmHg) (Fig. 6). MCF in the normally perfused area (LAD-area) increased by approximately 10% of the control (Fig. 5), and HR also increased slightly but significantly (by approximately 3%) (Fig. 8). The LVPP, SP,
Fig. 2. Changes in mean coronary perfusion pressure in Group I (○), Group II (△), Group III (●) and Group IV (▲). Experimental protocol is shown in Fig. 1. (*) represents a significant difference (P<0.05) at 15-min infusion of agents from the control values obtained just before infusion of agents, which are not significantly different among the groups. P value in the figure shows a significant difference compared with Group IV at 15-min infusion of agents. Vertical lines are standard errors of the means.

Fig. 3. Changes in coronary blood inflow. The values just before infusion of the agents (18.8±1.6, 21.5±1.7, 23.4±3.3 and 21.5±1.7 ml/min, respectively, in Group I, II, III and IV) are expressed as 100% (large ○). All other explanations are the same as described in Figs. 1 and 2.

and cardiac effort index tended to decrease (Figs. 8 and 7).

Partial coronary constriction under nipradilol infusion (Group IV) decreased both CBF and MCF in the underperfused area, and these levels were similar to that caused by partial coronary constriction alone (Group III) (Figs. 3 and 4). However, marked elevation in LVEDP in Group III was significantly alleviated by nipradilol (+1.8±0.7 mmHg) (Fig. 6). There was no significant difference between MCF after 5-min nipradilol infusion and that after the 15-min infusion with 10-min underperfusion (Fig. 4). MCF in the normally perfused area decreased by approximately 30% of the control (Fig. 5); and also similar decreases in LVPP, SP, HR and the cardiac effort index to those caused by nipradilol under normal coronary perfusion (Group II) were observed (Figs. 8 and 7).
Group IV and Group II shared similar features in all respects except for two: Group IV showed further decreases in CPP and CBF (Figs. 2 and 3).

Effects of nipradilol on high-energy phosphate compounds and lactate contents in underperfused canine myocardium: Myocardial contents of phosphate compounds (ATP, CP, Pi) and lactate in four groups are summarized in Table 1. Myocardial water contents were slightly higher in the subendocardium (ENDO) than in the subepicardium (EPI) in the underperfused area (78.8 ±0.2%, 77.8±0.5% and 78.0±0.2%, respectively, in inner, middle and outer layers in Group IV), but there were no significant changes among the four groups. Percentage changes in myocardial contents per wet weight of phosphate compounds and lactate were almost the same as those per dry weight.

Nipradilol under normal coronary perfusion (Group II) caused no significant changes in
Acute coronary stenosis in the absence of nipradilol (Group III) caused significant decreases in high-energy phosphate compound contents in all layers of the underperfused left ventricular free wall, while causing significant increases in Pi and lactate contents. The changes were more prominent in the inner layer, and CP and lactate especially exhibited significant falling and rising gradients, respectively, from the outer to inner layers. The contents per wet weight in the inner, middle and outer layers, with respect to the comparison of mean values between Group III and Group I (control group), respectively revealed the following: decreases of 32, 24 and 22% in the level of ATP; decreases of 75, 69 and 60% in the level of CP; increases of 1.9, 1.9 and 1.3 times the level of Pi; and increases of 4.3, 3.6 and 2.4 times the level of lactate.

Acute coronary stenosis in the presence of nipradilol (Group IV) caused significantly smaller decreases or increases in high-energy phosphate and lactate contents, respectively, in the underperfused myocardium than those without the presence of nipradilol. There were no significant decreases in ATP contents. CP contents still showed a transmural gradient. The contents per wet weight in the
LVPP | SP | HR
---|---|---
I | P < 0.01 | P > 0.05, P < 0.001 | I
II | I | II | III | IV
Group

Fig. 8. Left ventricular peak systolic pressure (LVPP), mean systemic blood pressure (SP) and heart rate (HR) at 15-min infusion of agents. The control values in Group I, II, III and IV are 127±7, 123±7, 135±14 and 122±6 mmHg in LVPP, 110±8, 103±4, 107±6 and 101±5 mmHg in SP, 168±15, 161±5, 157±7 and 158±11 beats/min in HR, respectively. All other explanations are the same as described in Figs. 1–3.

Table 1. Transmural high energy phosphates and lactate contents under normal perfusion and at 10-min coronary artery stenosis with and without npradilol in canine hearts

| Number of animals | ATP (µmol/g wet wt.) | CP (µmol/g wet wt.) | Pi (µmol/g wet wt.) | Lactate (µmol/g wet wt.) |
|-------------------|----------------------|---------------------|---------------------|-------------------------|
| Group I 6         | ENDO: 5.60±0.43      | 11.48±0.42          | 3.16±0.43           | 2.08±0.36               |
|                   | MID: 5.46±0.27       | 12.14±0.20          | 3.25±0.22           | 1.69±0.20               |
|                   | EPI: 5.30±0.34       | 12.17±0.33          | 3.92±0.47           | 1.72±0.26               |
| Group II 7        | ENDO: 5.38±0.13      | 10.61±0.57          | 3.72±0.24           | 1.88±0.23               |
|                   | MID: 5.31±0.18       | 11.61±0.72*         | 3.87±0.24           | 1.88±0.34               |
|                   | EPI: 5.60±0.17       | 11.73±0.43*         | 4.79±0.59           | 1.47±0.27               |
| Group III 6       | ENDO: 3.79±0.31b     | 2.82±0.24c          | 9.14±0.39           | 11.05±1.73*             |
|                   | MID: 4.14±0.34*      | 3.78±0.41*          | 9.30±0.40           | 7.76±1.18*              |
|                   | EPI: 4.13±0.25       | 4.84±0.51*          | 9.09±0.53           | 5.78±0.72*              |
| Group IV 6        | ENDO: 4.79±0.14c     | 6.74±0.83c          | 5.64±0.93           | 3.55±1.29               |
|                   | MID: 5.04±0.18c      | 8.54±1.28c          | 5.63±0.98           | 2.94±1.05               |
|                   | EPI: 4.93±0.35       | 9.88±0.79           | 5.34±0.64           | 2.12±0.42               |

Mean±S.E. Abbreviations: ENDO: subendocardium; MID: midcardium; EPI: subepicardium. Group I: saline, normal perfusion; Group II: nipradilol, normal perfusion; Group III: saline, underperfusion; Group IV: nipradilol, underperfusion. Other explanations are the same as described in Fig. 1. *Significantly different from the ENDO (P<0.05). a,b,c: Significantly different from the control: Group I (P<0.05, 0.01 and 0.001, respectively). Comparison between Group III and Group IV: Significantly different from Group III (P<0.05, 0.01 and 0.001, respectively).

inner, middle and outer layers, with respect to the comparison of mean values between Group IV and Group I, respectively revealed the following: decreases of 14%, 8% and 7% in the level of ATP; decreases of 41%, 30% and 19% in the level of CP; increases of 0.8, 0.7 and 0.4 times the level of Pi; and increases of 0.7, 0.7 and 0.2 times the level of lactate.

Discussion

Intravenous infusion of npradilol under normal coronary perfusion generally decreased cardiac functions. The hypotensive and cardiodepressive effects of npradilol in the present experiment are consistent with the results shown by Uchida (1). However, in contrast with his findings, LVEDP under no coronary constriction showed a slight elevation after npradilol infusion. This discrepancy cannot be explained by a difference of the dose used because npradilol in a dose over 100 µg/kg, i.v., causes a decrease in LVEDP, and in the present experiment, the total infused dose was 150 µg/kg, i.v.
although the method of the administration was different. Nipradilol is more potent as a $\beta$-adrenoceptor blocker than as an $\alpha$-adrenoceptor blocker or a vasodilator (1, 4, 7); and propranolol, which is 2 times less potent than nipradilol as a $\beta$-adrenoceptor blocker (7), given in the same dose as nipradilol easily elevates LVEDP in anesthetized dogs (1). Therefore, it is conceivable that in the present experiment, the $\beta$-adrenoceptor blocking effect of nipradilol was somewhat more prominent than its vasodilating effect. However, the degree of decrease in CBF and that in cardiac effort index reflecting cardiac oxygen consumption was similar. Myocardial contents of high-energy phosphates and lactate remained at the control levels. The results suggest that nipradilol under normal perfusion preserves the myocardial oxygen supply-demand relationship and myocardial energy metabolism.

In a previous study (10), we showed that the contents of high-energy phosphates (ATP, CP) in the myocardium are inversely correlated with the degree of myocardial ischemia. In the present experiment, the hypoperfused area at CPP of 30 mmHg induced by coronary stenosis showed a severe ischemic state. There was a significant accumulation of lactate and a decrease in CP content to below approximately one-third of the control in all layers. These results are consistent with the previous one (10) in which under these conditions the ST-segment of the epicardial ECG was also elevated. Oxygen supply in the area decreased below one-third of its normal level. On the other hand, the cardiac effort index (mean SP×HR) did not change. Increases in HR and in MCF in the normally perfused area produced by compensatory effects (15), at least in part, contribute to the absence of change in the cardiac effort index. The imbalance between myocardial oxygen supply and demand probably resulted in the significant metabolic changes in the underperfused area. It is probable that the metabolic derangement causes a marked decline in MCF in the underperfused area, which results in a marked elevation in LVEDP.

In addition, there were transmural gradients of the concentrations from the outer to the inner layers, that is, a more significant decrease in CP and a significant accumulation of lactate in the inner layer. The results are consistent with previous studies in which the inner myocardial layer of the left ventricle is more susceptible to damage by oxygen deficiency than is the outer layer (8–10, 16, 17). At CPP of 30 mmHg, autoregulation of coronary flow is abolished, and distribution of flow is directly dependent on gradient in myocardial tissue pressure (16). The transmural distribution of intramyocardial pressure depends on preload (17). The underperfusion of the inner layer of an ischemic area was probably augmented by a marked elevation in LVEDP, i.e., increased ventricular preload, which resulted in the significant metabolic gradients.

In the presence of nipradilol, the decrease in myocardial high-energy phosphates and the increase in lactate caused by the underperfusion were significantly retarded: the degree of changes in phosphate compounds and lactate decreased to $1/2$ (inner layer)–$1/3$ (outer) and $1/6$ (inner)–$1/10$ (outer), respectively, of that in the absence of nipradilol. The transmural gradient in CP content still remained, but the significant alleviation was also observed in the inner layer. The present results indicate that nipradilol significantly improves the ischemic derangement of myocardial energy metabolism in all layers affected by severe coronary stenosis. There were no significant differences between the absence and the presence of nipradilol with reference to the degree of decreases in CBF and MCF in the underperfused area. Concurrently, nipradilol significantly decreased the cardiac effort index and alleviated the marked elevation in LVEDP caused by acute coronary stenosis. Nipradilol seems to be differentiated by the latter effect from typical $\beta$-adrenoceptor blocking agents (1). Further research is needed to elucidate the role of the vasodilating property of nipradilol in improving energy metabolism in ischemic myocardium. However, these results indicate that excessive load in ischemic myocardium was significantly decreased by nipradilol. Thus, nipradilol probably induces a decrease in...
myocardial oxygen consumption and a favorable flow distribution, and therefore improves the transmural aerobic energy metabolism in the underperfused myocardium.

Nipradilol significantly decreased MCF and also the underperfusion itself resulted in a significant decrease in MCF in the area. The degree of decrease in both cases was similar. However, MCF in the underperfused area with nipradilol was maintained at the low level caused by nipradilol. The present results suggest, at least, that acute coronary stenosis in the presence of nipradilol does not cause a further deterioration in myocardial contractility. According to the metabolic changes, the inhibition in MCF in the underperfused area with nipradilol may be mainly due to the β-adrenoceptor blocking action, which is different from the inhibition mechanism in the underperfused area without nipradilol.

Acknowledgments: We are grateful to Kowa Co., Ltd., Tokyo, for providing nipradilol.

References
1 Uchida, Y.: Cardiovascular effect of 3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran (K-351). Japan. Heart J. 23, 981-988 (1982)
2 Asada, H., Nanjo, T., Itoh, T., Suzuki, H. and Kuriyama, H.: Effects of 3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran (K-351) on smooth muscle cells and neuromuscular transmission in guinea-pig vascular tissue. J. Pharmacol. Exp. Ther. 223, 560-572 (1982)
3 Kou, K., Kuriyama, H. and Suzuki, H.: Effects of 3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran (K-351) on smooth muscle cells and neuromuscular transmission in the canine mesenteric artery. Br. J. Pharmacol. 77, 679-689 (1982)
4 Ohira, A., Wada, M., Fuji, M., Nakamura, M., Kasuya, Y., Hamada, Y. and Shigenobu, K.: Effects of nipradilol (K-351) on alpha-adrenoceptor mediated responses in various isolated tissues. Arch. Int. Pharmacodyn. Ther. 278, 61-71 (1985)
5 Kou, K. and Suzuki, H.: The effects of 3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran (K-351) and its denitratred derivative on smooth muscle cells of the dog coronary artery. Br. J. Pharmacol. 79, 285-295 (1983)
6 Shirasawa, Y., Fuji, M. and Nakamura, M.: Venodilating action of nipradilol (K-351) in the pithed rat pretreated with dihydroergotamine. Japan. J. Pharmacol. 38, 77-82 (1985)
7 Uchida, Y., Nakamura, M., Shimizu, S., Shirasawa, Y. and Fuji, M.: Vasodative and β-adrenoceptor blocking properties of 3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran (K-351), a new antihypertensive agent. Arch. Int. Pharmacodyn. Ther. 262, 132-149 (1983)
8 Takenaka, F. and Higuchi, M.: High-energy phosphate contents of subepicardium and subendocardium in the rat treated with isoproterenol and some other drugs. J. Mol. Cell. Cardiol. 6, 123-135 (1974)
9 Higuchi, M.: Effects of nitroglycerin on transmural energy metabolism in the underperfused canine heart. J. Pharmacol. Exp. Ther. 222, 694-698 (1982)
10 Higuchi, M., Tomomatsu, E. and Nishi, K.: Transmural distribution of myocardial high energy phosphates and lactate in relation to the epicardial ECG in the underperfused canine heart. Pfluegers Arch. 391, 101-104 (1981)
11 Higuchi, M. and Asakawa, T.: Effects of nitroglycerin on regional myocardial function in the underperfused canine heart. J. Cardiovasc. Pharmacol. 7, 1087-1095 (1985)
12 Furchgott, R.F. and De Gubareff, T.: The determination of inorganic phosphate and creatine phosphate in tissue extracts. J. Biol. Chem. 233, 377-388 (1966)
13 Strehler, B.L.: Adenosine-5-triphosphate and creatine phosphate determination with luciferase. In Methods of Enzymatic Analysis, Edited by Bergmeyer, H.U., p. 559-572, Academic Press, New York (1965)
14 Hohorst, H.J.: L(+)-lactate. Determination with lactic-dehydrogenase and DPN. In Methods of Enzymatic Analysis, Edited by Bergmeyer, H.U., p. 266-270, Academic Press, New York (1965)
15 Theroux, P., Franklin, D., Ross, J., Jr. and Kemper, W.S.: Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ. Res. 35, 896-908 (1974)
16 Kjekshus, J.K.: Mechanism for flow distribution in normal and ischemic myocardium during increased ventricular preload in the dog. Circ. Res. 33, 489-499 (1973)
17 Archie, J.P.: Intramyocardial pressure: Effect of preload on transmural distribution of systolic coronary blood flow. Am. J. Cardiol. 35, 904-911 (1975)