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Effect of a Bradycardic Agent on the Isolated Blood-perfused Canine Heart

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Summary. **Bradycardic agents could limit the consequences of myocardial ischemia via two mechanisms: by decreasing myocardial oxygen demand (MVO_2) and by increasing diastolic coronary blood flow (CBF). We investigated whether the benzazepinon UL-FS 49 affects only sinus node cells or also smooth muscle and/or myocardial cells. To avoid confounding interactions with the periphery, we performed experiments on 11 isolated, blood-perfused canine hearts. Injection of UL-FS 49 (1 mg/kg i.c.) significantly reduced heart rate (HR) from 104 ± 7 to 93 ± 7 min^{-1} (mean ± SEM) and increased stroke volume (n = 6: 9.8 ± 1.1 vs. 13.2 ± 1.6 ml), so that cardiac output remained unchanged (n = 6: 1.1 ± 0.1 vs. 1.2 ± 0.1 l/min). The contractile state, assessed by isovolumic peak systolic pressure, was unaltered by UL-FS 49 (n = 5: 72 ± 6 vs. 72 ± 6 mmHg). At a constant coronary arterial pressure (CAP) of 80 mmHg, mean CBF was slightly decreased (102 ± 11 vs. 97 ± 10 ml/[min · 100 g]) by UL-FS 49, such that mean coronary resistance remained unchanged (0.9 ± 0.1 vs 1.0 ± 0.1 mmHg · min · 100 g/ml). The slight decreases in arteriovenous oxygen content difference (n = 6: 6.6 ± 0.7 vs. 6.5 ± 0.7 ml/100 ml) and in CBF lead to a calculated, significant decrease in MVO_2 (n = 6: 6.9 ± 0.5 vs. 6.0 ± 0.4 ml · 100 g/min). In conclusion, UL-FS 49 at the dose used decreases MVO_2 by reducing HR in isolated canine hearts. In the absence of negative inotropic and vasodilating effects, cardiac output is maintained via increased stroke volume, and CAP will likely be preserved in situ. Thus, this specific bradycardic agent could be useful in treating ischemic myocardial disease.**

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Key Words. **canine heart, cardiac output, bradycardic agent, UL-FS 49, coronary resistance, myocardial oxygen consumption, left ventricular contractility**

Depending on its duration and severity, ischemia induces acute ventricular dysfunction and finally irreversible myocardial damage. Because heart rate, wall tension, and contractile state are major determinants of myocardial oxygen demand [1], agents that reduce one or more of these factors hold promise in the treatment of myocardial ischemia. Beta-adrenoceptor blockers can reduce both the contractile state and heart rate in humans [2,3]. Calcium-channel blockers, on the other hand, also reduce the contractile state, decrease wall tension by reducing ventricular afterload [4,5], and increase oxygen supply to the ischemic myocardium by directly decreasing coronary resistance [6,7] and by blocking $alpha_2$-adrenoceptor-induced vasoconstriction [8]. However, decreases in contractile state could furthermore impair ischemic ventricular function, and the reduced afterload is likely to be associated with decreases in coronary arterial pressure.

Specific bradycardic agents act presumably solely on sinus-node cells, and thus could not only decrease oxygen demand, but also increase oxygen supply to the ischemic myocardium via an increased diastolic blood flow [9,10]. UL-FS 49 is a benzazepinon-type agent and is chemically related to verapamil [10,11]. Its negative chronotropic effects are well documented, both in isolated preparations [11,12] and in intact animals [10,13].

In order to investigate the direct effect of UL-FS 49 on heart rate, contractile state, cardiac output, coronary resistance, and myocardial oxygen consumption, independently of secondary effects via peripheral interactions, we performed experiments on isolated, blood-perfused canine hearts. For ethical reasons, all experiments reported in this study were performed at the end of other experiments, however, no other agents had been tested before.

Methods

General preparation

The supported isolated canine heart preparation was used as described previously [14]. Briefly, two mon-

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grel dogs of either sex (20–25 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.). The heart was removed from the donor dog, and perfused with blood from the support dog using a constant pressure perfusion pump (Figure 1). The perfusion in the aorta was retrograde via a cannula inserted in the left subclavian artery. Coronary arterial pressure was monitored by a cannula in the brachiocephalic artery.

After opening the left atrium and cutting all chordae tendineae, a thin-walled latex balloon was placed in the left ventricular cavity. An adaptor was sutured to the mitral annulus for connecting the ventricular balloon to the ventricular volume servopump. A microtip manometer (Millar, PC 380) was placed inside the water-filled balloon to measure left ventricular pressure. The space between the balloon and the ventricular wall was vented.

The coronary venous blood flow was measured by draining the unloaded right ventricle, i.e., the flow to both the right and left ventricle, and using an electromagnetic flowmeter (Narco Bio-systems, RT 400). Thus, the negligible portion of Thebesian blood flow [15] was ignored. The difference in arteriovenous oxygen content was continuously assessed by absorption spectroscopy [16].

Arterial PCO_2, PO_2, and pH of the support dog were maintained within the normal range. Arterial PO_2 was raised, if necessary, by enriching the inspired air with oxygen. The temperature of the perfusate was kept close to 38°C with the help of a heat exchanger.

Ventricular volume control system

A servosystem was used similar to that described previously [17]. In brief, the position of a plunger within a cylinder (Bellofram, SS-4-F-SM) was controlled by a linear motor (Ling Electronics, 411). The intraventricular balloon, the connecting tube, and the cylinder were filled with water. Thus, a change in ventricular volume was accompanied by a displacement of the plunger. A signal, derived from a plunger-attached linear displacement transducer, was compared with a volume-command signal. The difference was used as the error signal fed into a power amplifier (Crown, DC-300) to drive the linear motor (Figure 1).

Impedance loading system

The isolated left ventricles were afterloaded with the help of a computer-based system, similar to that described previously [18]. In brief, a personal computer was programmed with the differential equations of the three-element Windkessel model that has recently been shown to reasonably represent the impedance spectra of the real arterial system [19]. Filling of the ventricle was also realized by the computer-based system that switched to a simple filling circuit during diastole.

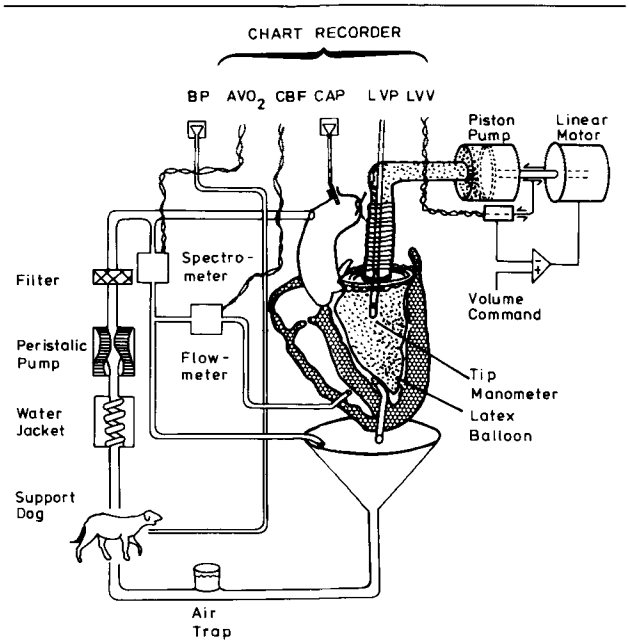

Fig. 1. Schematic diagram of the isolated canine heart preparation. Coronary perfusion was maintained with blood from a support dog. The left ventricular cavity was fitted with a balloon that was connected to a piston pump. The ventricular cavity volume was set and controlled by a servomotor connected with the piston pump. BP = blood pressure; AVO_2 = arteriovenous difference in oxygen content; CBF = coronary blood flow; CAP = coronary arterial pressure; LVP = left ventricular pressure; LVV = left ventricular volume.

Experimental protocol

Experiments were conducted on a total of 11 isolated canine hearts. Measurements were performed during control conditions and on average after 2 minutes when steady-state conditions were achieved after intracoronary administration of 1 mg/kg UL-FS 49 to the isolated heart. In previous studies on canine hearts, UL-FS 49 was administered at a dose of 1 mg/kg to observe a distinct effect on heart rate [11,20]. In turn, the effect of the agent on contractility in isolated guinea pig atria was considerably higher (* 1000) than it was on heart rate [11]. We wanted to investigate both the effect on heart rate, coronary resistance, and contractility, and therefore decided for a relatively high dose.

To evaluate the effect of UL-FS 49 on the left ventricular contractile state, five isolated hearts were made to contract isovolumically. Six other isolated hearts were made to eject a physiologic afterload resistance of 3.0 mmHg · min/ml.

The difference in arteriovenous oxygen content was assessed in six hearts. In all hearts, coronary arterial pressure was kept constant close to 80 mmHg with the help of a peristaltic pump.

For normalizing coronary blood flow to 100 g left ventricular weight and for calculation of ventricular oxygen consumption, both the right and the left ventricle were weighed at the end of each experiment.

Data acquisition

Left ventricular pressure, ventricular volume, aterio-venous difference in oxygen content (A-VOX System), coronary venous blood flow (Narco Bio Systems, RT400), coronary arterial pressure (Statham, P23Db), and arterial pressure of the support dog (Statham, P23Db) were continuously recorded on a forced-ink chart recorder (Gould, Recorder 2800). The A-VOX system measures the oxygen saturation by means of spectrophotometry. Because the device consists entirely of solid-state components, its calibration is permanent [16]. Thus, we did not recalibrate our new A-VOX system and disregarded any aging of the photodiodes that, very unlikely, might have occurred during the short duration of this experimental study.

Calculations and statistical analysis

Data were analyzed from chart recordings made at a paper speed of 50 mm/s. All calculations involving pulsatile variables were performed using averages of between four and six consecutive beats.

Myocardial oxygen consumption was calculated according to Fick's principle as the product of the mean coronary venous flow and the arteriovenous difference in oxygen content. Coronary venous flow was normalized to 100 g left ventricular weight. Coronary resistance was calculated as the ratio between coronary arterial pressure and normalized coronary blood flow.

Because of the small sample sizes in this study, data very unlikely were normally distributed. Therefore, Wilcoxon's nonparametric signed rank test was used to compare hemodynamic variables before and after administration of UL-FS 49. A $p-$ value less than 0.05 was considered to indicate statistical significance. Data are reported as mean values ± SEM.

Results

The 11 isolated right and left ventricles weighed on average 153 ± 6 g and the left ventricles 116 ± 5 g. Thus, the right ventricle weighed on average 24% of the ventricular mass.

On average, the protocol of this study was started 120 ± 40 minutes after completion of the first protocol. To compare the hemodynamic state before the onset of the first and this protocol, four hemodynamic variables were assessed: The heart rate remained essentially unchanged (100 ± 19 vs. 104 ± 25 min^{-1}) as well as the end-diastolic pressure (7.0 ± 5.3 vs. 8.7 ± 4.6 mmHg). The contractile state was measured in terms of the slope of the end-systolic pressure-volume relation (E_{es}). This variable increased significantly from 3.9 ± 1.3 to 4.2 ± 1.1 mmHg/ml; n = 6). The coronary resistance exhibited some time dependency and decreased insignificantly from 1.11 ± 0.23 to 0.90 ± 0.32 mmHg/(ml/min/100 g).

Regarding hemodynamic data (Figure 2), intracoronary administration of 1 mg/kg UL-FS 49 decreased the heart rate on average by 11%, from 104 ± 7 to 93 ± 7 min^{-1}. Five ventricles contracted isovolumically at an intraventricular volume of 20.2 ± 4.2 ml. In these ventricles the peak left ventricular pressure was nearly identical before and after administration of the agent (72 ± 6 vs. 72 ± 6 mmHg). In six ventricles that were ejecting against a constant afterload impedance, peak left ventricular pressure decreased insignificantly from 76 ± 8 to 70 ± 7 mmHg. In these ventricles, the decrease in heart rate was accompanied by both a significant increase in stroke volume (9.8 ± 1.1 vs. 13.2 ± 1.6) and ejection fraction (25.5 ± 2.7 vs. 34.1 ± 4.2%). As a result of comparable decreases in heart rate and increases in stroke volume, the cardiac output remained essentially the same (1.1 ± 0.1 vs. 1.2 ± 0.1 l/min).

In all 11 ventricles, mean coronary arterial pressure was held constant before and after administration of UL-FS 49 (81 ± 4 vs. 83 ± 4 mmHg). After injection of the agent, mean coronary venous flow was essentially unchanged (102 ± 11 vs. 97 ± 10 ml/(min · 100 g), as was mean coronary resistance (0.9 ± 0.1 vs. 1.0 ± 0.1 mmHg · min · 100 g/ml) (Table 1).

The arteriovenous difference in oxygen content (Table 1) was measured in one isovolumically contracting and in five ejecting ventricles. Together the slight decreases in this variable (6.6 ± 0.7 vs. 6.5 ± 0.7 ml/100 ml) and in coronary venous flow lead to a calculated significant decrease in myocardial oxygen consumption by 13% (6.9 ± 0.5 vs. 6.0 ± 0.4 ml · 100 g/min; Table 1).

Discussion

Any attempt to extrapolate the effects of a cardiac agent from in vitro studies to in vivo conditions is fraught with difficulties. The in vitro effects of the agent will be the result of a complex summation of direct myocardial effects, interactions between the heart and vasculature, and reflexes affecting neuro-

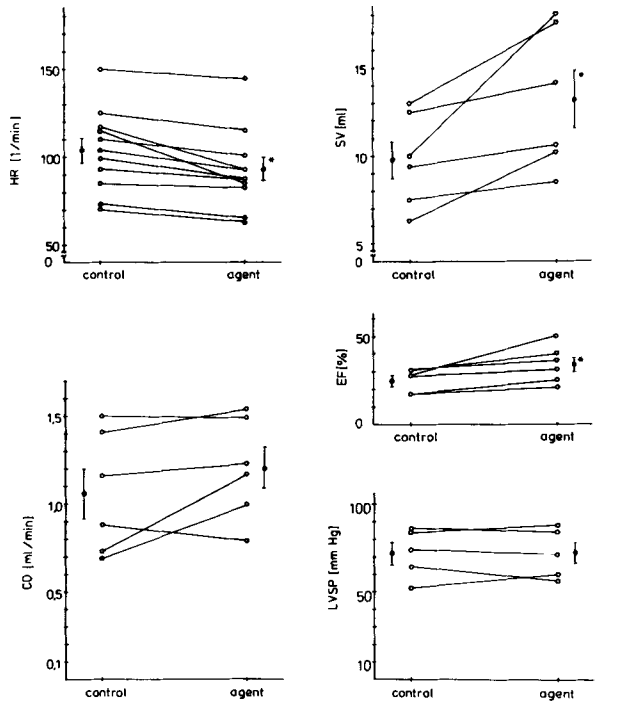

*Fig. 2. Effect of UL-FS 49 (1 mg/kg i.c.) on ventricular function of isolated canine hearts. The agent decreased heart rate (HR) in all ventricles, and increased stroke volume (SV) and ejection fraction (EF) in ejecting ventricles significantly, whereas cardiac output changed insignificantly. The ventricular contractile state, assessed in terms of peak systolic pressures in isovolumically contracting ventricles, remained unchanged. * $p < 0.05$.*

***Table 1.** Effect of UL-FS 49 (1 mg/kg i.c.) on coronary blood flow (CBF, ml/[min · 100 gl) and mean coronary resistance (R, mmHg · min · 100 g/ml) of isolated canine hearts*

#	CBF	R	AVO_2	MVO_2
Control				
1	84.4	1.05	8.3	7.0
2	123.8	0.81	·	·
3	51.9	1.35	·	·
4	86.6	1.11	8.0	7.0
5	181.3	0.32	4.4	7.9
6	64.0	1.22	·	·
7	132.2	0.54	·	·
8	130.2	0.71	6.0	7.8
9	96.3	0.87	7.5	7.2
10	89.2	0.84	5.1	4.5
11	90.0	0.88	·	·
Sum	102.7 ± 11.0	0.88 ± 0.09	6.6 ± 0.7	6.9 ± 0.5
UL-FS 49				
1	77.3	1.15	8.3	6.4
2	125.1	0.86	·	·
3	47.2	1.61	·	·
4	61.9	1.56	8.6	5.3
5	157.5	0.38	4.7	7.4
6	75.4	1.05	·	·
7	125.9	0.56	·	·
8	113.8	0.82	5.0	5.7
9	96.3	0.88	6.8	6.5
10	83.2	0.88	5.5	4.6
11	99.0	0.81	·	·
Sum	96.6 ± 9.7	0.96 ± 0.11	6.5 ± 0.7	6.0 ± 0.4

Neither variable changed significantly. Both the insignificant decreases in arteriovenous oxygen content difference (AVO_2, ml/100 ml) and in coronary blood flow lead to a significant calculated decrease in myocardial oxygen consumption (MVO_2, ml · 100 g/min).
[1]$p < 0.05$.

genic drive to the heart. However, owing to the recirculating blood, the isolated heart is not completely insensitive to neurogenic mechanisms, i.e., overflowing catecholamines. In this study, these effects presumably were minor, because coronary blood flow of the isolated heart (i.e., withdrawal rate from the support dog) only varied moderately, and heart rate of the support dog was almost unaffected before and after administration of the agent (103 ± 28 vs. 100 ± 28 min^{-1}).

To elucidate the genuine effects of the agent, the measurements of this study were performed using isolated, blood-perfused canine hearts. This experimental model has been employed in our laboratory for studying the end-systolic pressure-volume relation as an index of contractile state [21], for investigating the energetics of ventricular contraction [22], and for assessing the effects of a cardiac agent, a second-generation calcium blocker, on ventricular hemodynamics [23].

At first sight, the preparation seems to present a failing heart with a peak left ventricular pressure that averaged 74 mmHg for all ventricles and an ejection fraction of 25% for the ejecting ventricles. However, the volume load of the ventricles was held rather low, such that the end-diastolic pressure averaged 8.7 ± 4.6 mmHg before and 8.8 ± 4.2 mmHg after administration of the drug, i.e., the ventricles were operating on a low ventricular performance level.

From an ethical point of view, we feel that the purpose of this study justifies performing experiments after the conclusion of other experiments that do not counterfeit the results. In fact, there are no experiments included in this study where the experimental preparation was obviously deteriorated or where drugs, other than anesthetics, were already aboard. Both the unchanged heart rate of the isolated heart, and its systolic and diastolic properites (in terms of the slope of the end-systolic pressure-volume relationship and the end-diastolic pressure), after completion of the first protocol confirm the stability of the preparation. Although the coronary resistance decreased

insignificantly by about 19%, the coronary reserve was obviously not exhausted.

Effect on heart rate

Injection of UL-FS 49 significantly reduced heart rate in isolated hearts. In contrast to earlier study on conscious dogs [11], the heart rate reductions in this study were not positively correlated with the control heart rate. This might very well be owing to the wider range of heart rates under investigation in their study (80–250 min^{-1}) as compared to our more limited range with lower heart rates (65–150 min^{-1}). The heart rate in a denervated preparation would not be expected to vary that much. However, the isolated heart receives blood from the support dog in this preparation, and thus, the heart rate will depend, additionally, on anesthesia and on overflowing catecholamines.

UL-FS 49 had a relatively small effect on the heart rate of the isolated hearts. This could be due partly to the experimental preparation in which blood flow to the atria might be impeded as a result of surgical interventions (e.g., for suturing an adaptor to the mitral annulus, the left atrium needs to be opened). Thus, the response of sinus node cells to the bradycardic agent could have been attenuated due to slight ischemia.

It was not so much the aim of this study to show, once more, the potency of the agent to reduce heart rate. Instead, we wanted to investigate the effects on the myocardium and on the coronary resistance independently from peripheral interactions. Hence, the weak bradycardia does not invalidate the conclusion of this study. In addition, even those moderate decreases in heart rate were associated with significant decreases in myocardial oxygen consumption, thus confirming the close association of this variable with heart rate [2,24].

Effect on myocardium

The effect of UL-FS 49 on ventricular contractile state in dogs has been described, so far, in terms of changes in left ventricular dP/dt_{max} [10,13,20]. However, this index not only reflects changes in contractile state, it is also positively correlated with heart rate [25,26] and preload [25,27]. Therefore, bradycardia would be expected to decrease dP/dt_{max}, whereas prolonged diastole would increase ventricular preload, and concomitantly, dP/dt_{max}. Thus, constancy of this index could possibly result from these two counteracting correlations.

We assessed left ventricular contractile state by measuring the peak systolic pressure of isovolumically contracting hearts. At constant preload and afterload, we found no change in left ventricular peak systolic pressure. The increase in stroke volume and ejection fraction in the ejecting hearts additionally support the finding that UL-FS 49 does not impair ventricular performance such that cardiac output, i.e., the in situ blood flow to the organs, is maintained.

Effect on coronary resistance

The direct effects of intracoronary UL-FS 49 on the resistance of the coronary vascular bed are not known, so far. Since the coronary resistance in the intact coronary bed is predominantly determined by the small resistive vessels [28], our results indicate that UL-FS 49 does not affect these vessels.

With an coronary arterial pressure of 80 mmHg at an average peak left ventricular pressure of 74 mmHg, the hearts seem to be constantly overperfused. This, together with an unchanged coronary resistance at reduced MVO_2 after reduction of heart rate, might suggest the lack of metabolic control of coronary resistance. Thus, any dilating effect of the agent could be absent if the coronary reserve were already exhausted in this preparation. A coronary blood flow of about 100 ml/min and 100 g ventricular weight and a coronary resistance close to 1 mmHg/(ml/min) represent physiologic values for hearts in anesthetized dogs [29,30]. Because our hearts were working in a lower range of ventricular performance, a value of 1 mmHg/(ml/min) for coronary resistance seems to be low. However, the calculations in this study do not consider the right ventricular weight that averaged 24% of the total weight. Hence, actual blood flow to the left ventricle was proportionally smaller, resulting in a coronary resistance higher than the given numbers, i.e., than 1 mmHg/(ml/min). Corrections for the right ventricular weight were not performed, because there was no appropriate method and because the right ventricle contracted isotonically, a mode that was not changed throughout the experiment.

To additionally test whether the coronary reserve was exhausted, we infused in four hearts adenosine (1 mg/min) in the perfusion line. On average, the coronary resistance decreased from 0.9 to 0.3 mmHg/(ml/min). This decrease and a basal resistance value higher than 1 mmHg/(ml/min) for the left ventricle suggests that our experimental preparation very likely was operating in the autoregulatory pressure-coronary flow range.

Guth and colleagues [20] already suggested that UL-FS 49, as a chemical congener of verapamil, might have a coronary vasodilator effect. We did not observe major changes in the coronary resistance. However, this does not necessarily rule out such vasodilator properties, since they could have been obscured by

a concomitant vasoconstriction owing to the reduced myocardial oxygen consumption. Because of the relatively modest reduction of this variable, we conclude that a vasodilator effect should likewise be modest.

Coronary resistance, and hence blood flow, is also influenced by an extravascular component [31,32] that, in part, depends on heart rate and wall tension [33]. This extravascular component is maximal during systole, so that coronary inflow occurs predominantly during diastole [34]. Thus, bradycardia not only decreases coronary resistance via decreasing heart rate but, additionally, increases the ratio of diastole to cardiac cycle.

With these considerations in mind, the coronary resistance in the isolated hearts should have decreased. Instead, we found no major change in this variable. This might in part be due to the fact that reductions in heart rate were only moderate in the isolated hearts. Moreover, the beneficial effect of reduced heart rate on the extravascular component is counteracted, to a certain extent, by an increased extravascular component via increased diastolic filling and wall tension in the ejecting hearts. The moderate increase in coronary resistance in our experiments could, on the other hand, also be secondary to the decreased oxygen consumption. The effect of a bradycardic agent on vascular smooth muscle contrasts with effects of calcium-channel blockers that are used for the treatment of myocardial ischemia and are reported to decrease ventricular afterload [4,5,23] and thus will reduce wall tension. Also in contrast to UL-FS 49, calcium-channel blockers decrease coronary resistance by direct action on coronary smooth muscle cells [6,23,30]. Because UL-FS 49 seems to be devoid of such actions on smooth muscle cells, it will not furthermore impair coronary arterial pressure.

Effect on myocardial oxygen demand-supply balance

Heart rate and ventricular afterload cannot be discussed with regard to their effect on coronary resistance, which will primarily determine myocardial oxygen supply. Heart rate, in addition, is an extremely important determinant of myocardial oxygen demand [1,24]. Beta-adrenoceptor blockers [35,36], some calcium-channel blockers and UL-FS 49 effectively reduce heart rate, and thus, are useful in the treatment of coronary heart disease. Beat-to-beat myocardial oxygen demand depends, in turn, on peak wall stress [1], and thus, on contractile state and afterloading. Both beta-adrenoceptor blockers and calcium-channel blockers [7] decrease the ventricular contractility, and in consequence, myocardial oxygen demand. However, this beneficial action might be antagonized by further impairment of ischemic ventricular performance, such as decreased cardiac pump function. Our data demonstrate that UL-FS 49 is devoid of negative inotropic effects and therefore does not decrease cardiac output. The increase in stroke volume in the isolated hearts in this study, together with the reduced heart rate, are suggestive of increased diastolic filling, and hence, in wall stress in the ejecting hearts. Since global myocardial oxygen consumption was significantly reduced, the latter effect seems to play a minor role on oxygen demand in this study.

However, our way of calculating myocardial oxygen consumption will have introduced a systematic error: The right ventricular weight was not included in the calculation of the normalized blood flow, and consequently, this variable and the values given for the left ventricular oxygen consumption are too high. Because the right ventricular mass averaged only about 24% of the total ventricular weight and the right ventricle was kept unloaded throughout the experiment, the right ventricular oxygen consumption was relatively low, and this portion, very likely, did not vary.

Calcium-channel blockers decrease myocardial oxygen demand via dilating peripheral vasculature, and thus, ventricular afterload [4,5]. On the other hand, decreases in mean blood pressure, and likewise in coronary arterial pressure, could reduce myocardial oxygen supply by decreasing myocardial perfusion and ischemic coronary flow. In contrast to calcium-channel blockers, UL-FS 49 in this study did not increase coronary blood flow (and oxygen supply) at constant coronary aterial pressure. This is not necessarily a disadvantage: Because the coronary reserve distal to a severe stenosis on a coronary artery is already exhausted [37], calcium-channel blockers will particularly dilate intact coronary arteries, thus inducing a flow redistribution and "stealing" blood flow from the ischemic region [30]. This latter property was challenged after it had been demonstrated that calcium-channel blockers could also preferentially increase ischemic subendocardial blood flow [38].

It might be misleading to choose a drug for treating coronary heart disease solely on the basis of its efficacy to enhance *mean* myocardial blood flow. During myocardial ischemia, the subendocardial layer is especially jeopardized [39,40]. Thus, oxygen supply to this region needs to be augmented. Because coronary inflow occurs predominantly during diastole, both beta-adrenoceptor blockers and some calcium-channel blockers will increase blood flow to the subendocardial layer via negative chronotropy. As a result of a massive decline in coronary arterial pressure, the myocardium could become underperfused with these agents

[7]. On the other hand, it was also shown that calcium antagonists can preferentially increase ischemic subendocardial blood flow [38]. Specific bradycardic agents will act in a comparable fashion that will be accompanied, however, by maintained coronary arterial pressure, as found in this study on isolated canine hearts and in a previous study in conscious dogs [11]. Thus, such agents can effectively increase poststenotic myocardial oxygen supply, particularly to the subendocardium [10,20], and prevent exercise-induced poststenotic myocardial dysfunction [13,20].

We conclude that, at the dosage used, UL-FS 49 acts selectively on sinus node cells and therefore decreases myocardial oxygen demand by reducing heart rate, and concomitantly increasing oxygen supply by enhancing diastolic inflow. Since the agent is devoid of negative inotropic effects, cardiac pump function is maintained and ischemic ventricular function will not be further impaired. Because the agent does not dilate the coronary arterial and the peripheral bed, and in consequence, does not decrease coronary arterial pressure, transmural flow redistribution is prevented and oxygen supply to the subendocardium is maintained. Thus, this specific bradycardic agent seems to provide an alternative approach for treating myocardial ischemia.

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