Effects of a Bradycardic Agent (DK-AH 269) on Haemodynamics and Oxygen Consumption of Isolated Blood-Perfused Rabbit Hearts

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A. Granetzny, U. Schwanke, E. Gams, J. D. Schipke

Objectives: Pharmacologic bradycardia is a promising strategy to improve myocardial energetic balance. We evaluated the effects of the novel sinus node inhibitor DK-AH 269 (DK) on ventricular function and perfusion in isolated rabbit hearts.

Methods: To differentiate between the effects of the negative force-frequency relation and a direct negative inotropic action of DK, measurements of haemodynamic and metabolic parameters were made during electrical pacing (EP), after application of DK (DK+EP), and after termination of pacing (DK–EP).

Results: Heart rate was significantly reduced by DK (EP: 161 ± 20, DK+EP: 161 ± 19 min⁻¹, DK–EP: 101 ± 32 min⁻¹, mean ± SD, p = 0.02). In parallel, diastole significantly lengthened without pacing (EP: 241 ± 35, DK+EP: 234 ± 38, DK–EP: 459 ± 220 ms, p = 0.04). Aortic flow was decreased in the presence of DK (EP: 40.6 ± 21.7, DK+EP: 32.8 ± 17.9 ml/min) and even further in the absence of pacing (DK–EP: 22.8 ± 24.6 ml/min). However, stroke volume (EP: 0.31 ± 0.16, DK+EP: 0.26 ± 0.14 ml) and peak isovolumic left ventricular pressure (EP: 109 ± 19, DK+EP: 92 ± 20, mmHg) were only moderately reduced. DP/dt max remained essentially unchanged after DK (EP: 1355 ± 545, DK+EP: 1390 ± 830 mmHg/s), but decreased without pacing (DK–EP: 890 ± 500 mmHg/s). DP/dt min, as a measure of early relaxation, had a tendency to decrease after DK with and without pacing (EP: –1245 ± 625, DK+EP: –1055 ± 410, DK–EP: –725 ± 340 mmHg/s), while the left ventricular end-diastolic pressure remained unchanged after DK and significantly decreased without pacing (EP: 10 ± 7, DK+EP: 9 ± 6, DK–EP: 5 ± 5 mmHg, p = 0.03). Coronary blood flow (CBF) decreased from 204 ± 29 to 156 ± 21 ml/min/100 g with DK and remained almost constant without pacing (148 ± 33 ml/min/100 g). The relation between subendocardial and subepicardial flow (colored microspheres) decreased slightly with DK (EP: 1.46 ± 0.39, DK+EP: 1.40 ± 0.28, DK–EP: 1.36 ± 0.41). The myocardial oxygen consumption (MVO₂) decreased with DK and further without pacing (EP: 9.8 ± 3.0, DK+EP: 8.7 ± 3.0, DK–EP: 6.2 ± 3.8 ml/min/100 g).

Conclusions: DK effectively reduced HR and prolonged diastole. The drug has no major negative inotropic effect, reduces MVO₂ and permits, in parallel, CBF to fall. In consequence, this novel bradycardic agent could prevent tachycardia in the experimental setting or could prevent unwanted, postoperative tachycardia. In addition, it could be an effective approach to induce bradycardia for off-pump coronary operations without compromising left ventricular function.

Key words: isolated blood-perfused heart, systolic and diastolic function, bradycardia, rabbit, oxygen consumption

Figure 1. Mechanism of action of DK-AH 269 (for explanation see text; from [11], with permission)
hearts, we described a dose-dependent reduction in heart rate by DK together with a prolongation of diastole [13, 14]. From these experiments and from others [11], however, it was unclear whether (1) that agent per se compromises myocardial inotropic performance, or whether the decreased function was due (2) to the negative force-frequency relation (= negative staircase phenomenon [15, 16]) or (3) to a time-dependent deterioration of the experimental model. To differentiate whether one or more of these effects were involved, experiments were performed on isolated, blood-perfused rabbit hearts that were paced before and after administration of DK. Additional measurements were made after pacing was terminated.

Methods

Experiments were performed on 10 isolated hearts of male New Zealand White rabbits with an average age of 7 months; body mass ranged from 2500 to 3500 g. The rabbits were handled according to the animal welfare regulations of the German federal authorities which are in accordance with Guide for the Care and Use of Laboratory animals (NIH publication #85–23, revised 1985). The animals were anaesthetized with 25 mg/kg i.m. ketaminhydrochloride and 5 mg/kg xylazine. After muscular relaxation (pancuronium-bromide 0.4 mg/kg) and tracheotomy, artificial respiration was performed with a small-animal respirator (Ugo-Basile, 7025). After thoracotomy and pericardiotomy, the hearts were rapidly excised and without intermittent ischaemia were arrested using saturated potassium chloride. To normalize blood flow both left and right ventricles were weighed.

The heart rate during electrical pacing before (EP) and after (DK+EP) administration of 10⁻⁶ M DK-AH 269 (DK) was administered at a concentration of 10⁻⁶ M, and measurements were repeated after 30 min. After termination of pacing, the measurements were repeated. To evaluate the regional myocardial flow, colored microspheres were injected after vigorous mixing (Vibrofix, IKA-Labortechnik) during each of the three experimental steps, ie during electrical pacing, after DK, and without pacing. The temperature of the heart was kept constant at 38.5 °C. At the end of each experiment, the hearts were arrested using saturated potassium chloride. To normalize oxygen consumption and arterio-venous difference in oxygen content.

The heart rate during electrical pacing before (EP) and after (DK+EP) administration of 10⁻⁶ M DK-AH 269 (DK) was 161 ± 20 and 161 ± 19 min⁻¹ respectively. Without pacing (DK–EP), heart rate significantly decreased to 101 ± 32 min⁻¹ (Fig. 3, p = 0.02). In parallel, at unchanged length of systole,
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the duration of diastole was maintained or increased respectively (EP: 241 ± 35, DK+EP: 234 ± 38, DK–EP: 459 ± 220 ms, p = 0.04). Aortic flow decreased by 19% from 40.6 ± 21.7 to 32.8 ± 17.9 ml/min in the presence of DK and without pacing by an additional 30% to 22.8 ± 24.6 ml/min (n.s.). Stroke volume was moderately reduced (EP: 0.31 ± 0.16, DK+EP: 0.26 ± 0.14 ml) and was further reduced to 0.21 ± 0.25 ml without pacing. Peak left ventricular isovolumic pressure exhibited a tendency to decrease during the three experimental steps from 109 ± 19 to 92 ± 20.3 to 75 ± 25 mmHg (Fig. 4, top). DP/dtmax as measure of contractile state, remained unchanged after administration of the agent (1355 ± 545 vs. 1390 ± 830 mmHg/s) and was decreased without pacing (890 ± 500 mmHg/s; n.s.) (Fig. 4, bottom). DP/dtmin was decreased with DK and furthermore without pacing (EP: −1245 ± 625, DK+EP: −1055 ± 410, DK–EP: −725 ± 340 mmHg/s). The time constant of pressure decay (τ) was slightly reduced with DK (EP: 40.6 ± 9.0, DK+EP: 35.3 ± 4.9 ms) and almost recovered without pacing (38.7 ± 6.5 ms). The left ventricular end-diastolic pressure was 10 ± 7 mmHg during control and remained almost unchanged in the presence of the agent (9 ± 6 mmHg). The decrease to 5 ± 5 mmHg after termination of pacing was significant (Fig. 5, p = 0.03). In parallel, the end-diastolic left ventricular diameter was decreased (EP: 10.07 ± 0.9, DK+EP: 9.89 ± 22, DK–EP: 9.39 ± 9.3 mm), ie preload was reduced. The global coronary blood flow was reduced from 204 ± 29 to 156 ± 21 to 148 ± 33 ml/min/100 g in the three experimental steps (Fig. 6, top). No significant transmural redistribution paralleled these changes: the ratio between subendocardial and subepicardial flow only slightly decreased (EP: 1.46 ± 0.39, DK+EP: 1.40 ± 0.28, DK–EP: 1.36 ± 0.41).

Figure 3. The heart rate (HR) was significantly reduced with DK. Mean ± SD during pacing (EP), DK-AH 269 10−6 M (DK+EP) and without pacing (DK–EP), *p = 0.02

Figure 4. The peak left ventricular pressure (LVP max) was reduced with DK (top); dp/dtmax was constant with DK+EP and was diminished without pacing (bottom). Mean ± SD during pacing (EP), DK-AH 269 10−6 M (DK+EP) and without pacing (DK–EP)

Figure 5. The end-diastolic left ventricular pressure (LVP ) was significantly decreased with DK after pacing was terminated. Mean ± SD during pacing (EP), DK-AH 269 10−6 M (DK+EP) and without pacing (DK–EP), *p = 0.03

Figure 6. The global coronary blood flow (CBF) was reduced with DK+EP and remained constant after pacing was terminated (top) while the coronary blood flow per beat (CBF/beat) was increased in the last experimental step (bottom). Mean ± SD during pacing (EP), DK-AH 269 10−6 M (DK+EP) and without pacing (DK–EP)
The administration of DK (peak left ventricular pressure and rate, systolic function was only moderately reduced after myocardial contractility [11]. At a constantly held heart consequence, heart rate reduction can cause a reduction of the force-frequency relation (= staircase phenomenon) Systolic function

Tail-dome filling and/or a lower end-diastolic pressure. On the other hand, myocardial perfusion should be improved since myocardial inflow – which occurs predominantly in diastole – should be increased [23]. During pacing at control rate, systolic function almost completely recovered, thus, nicely demonstrating the effects of the negative force-frequency relation in non-failing hearts.

The effects of the negative staircase phenomenon were again corrected for the time-dependent deterioration (ca. 75 min), the pure effect of the negative staircase phenomenon was less pronounced: left ventricular peak pressure and stroke volume decreased by only 6 and 4 %, respectively. While the decrease in dP/dt\text{max} (~25 %) was considerably more pronounced, it must be remembered that this measure not only reflects changes in contractile state but also depends on heart rate [26–28]. From these data we conclude that the considerably decreased heart rate was associated with an only moderately decreased systolic function in non-failing hearts. In failing human myocardium, frequency-induced potentiation of contractile force was found to be blunted or inverse [29]. We postulate from these findings that bradycardic agents either do not affect or do even improve systolic function.

The present data on the inotropic effects of DK are in concert with results from previous studies in which UL-FS 49 was used. In a study on isolated pig hearts, heart rate and in parallel, systolic function were reduced after administration of that agent [23]. During pacing at control rate, systolic function almost completely recovered, thus, nicely demonstrating the effects of the negative force-frequency relation in non-failing hearts.

Systolic function

The force-frequency relation (= staircase phenomenon) relates the contractile state to heart rate [15, 16, 24]. As a consequence, heart rate reduction can cause a reduction of myocardial contractility [11]. At a constantly held heart rate, systolic function was only moderately reduced after administration of DK (peak left ventricular pressure and stroke volume both by 16 % and dP/dt\text{max} unchanged).

In a former study using the same experimental model [25], the time-dependent deterioration of left ventricular function after administration of buffer was assessed. After a comparable duration of the protocol (ca. 45 min), left ventricular peak pressure, stroke volume and dP/dt\text{max} were decreased by 8, 12 and 6 %, respectively, whereas heart rate remained unchanged. Thus, the change seen after DK in part be attributed to the functional decay of the experimental model, and we exclude a major negative inotropic effect of DK in our experimental model.

If, however, electrical pacing was terminated and heart rate was allowed to decrease (37 %), systolic function was clearly decreased: peak left ventricular pressure, stroke volume and dP/dt\text{max} were all decreased (18, 19, and 36 %). If these measures of systolic function were again corrected for the time-dependent deterioration (ca. 75 min), the pure effect of the negative staircase phenomenon was less pronounced: left ventricular peak pressure and stroke volume decreased by only 6 and 4 %, respectively. While the decrease in dP/dt\text{max} (~25 %) was considerably more pronounced, it must be remembered that this measure not only reflects changes in contractile state but also depends on heart rate [26–28]. From these data we conclude that the considerably decreased heart rate was associated with an only moderately decreased systolic function in non-failing hearts. In failing human myocardium, frequency-induced potentiation of contractile force was found to be blunted or inverse [29]. We postulate from these findings that bradycardic agents either do not affect or do even improve systolic function.

Diastolic function

The effect of heart rate on myocardial relaxation has been carefully studied, but the results are not consistent. Whereas heart rate changes only slightly affect the time constant of left ventricular pressure decay (τ) [30], this measure was decreased if heart rate was increased [31]. Similarly, the impaired dP/dt\text{min} after DK was more likely due to the reduced heart rate rather than to a direct drug effect on early relaxation. In contrast to the further reduction of dP/dt\text{min} after termination of pacing, τ remained nearly constant in this study. Likely, τ is less heart-rate-dependent than dP/dt\text{min} [30]. Additional results from
a study on isolated pig hearts treated with UL-FS 49 support the notion that the benzazepine-type agents do not affect coronary perfusion in that study, neither dP/dt max nor τ were significantly affected [8].

End-diastolic ventricular filling is inversely related to heart rate, as shown by vagal or atrial stimulation [32]. The prolonged diastole positively influences left ventricular filling [33], which, in turn, will affect end-diastolic pressure. Bradycardic agents must hereby not necessarily change diastolic pressure [8] and, therefore, the variable findings suggest that methodological aspects (experimental model, working point on the end-diastolic pressure-volume curve, degree of bradycardia) represent important factors in determining the effects of bradycardic agents on the end-diastolic pressure. Thus, the decreased end-diastolic pressure after DK without pacing in this study fits the concept that a reduction in heart rate is associated with a more complete late ventricular relaxation.

Global and regional coronary blood flow, myocardial oxygen consumption

Heart rate reduction with sinus node inhibitors such as alinidine [34], zatebradine [21, 23], or DK-AH 269 [11–13] is associated with a prolonged diastole, and thus, should allow an increase in coronary blood flow if it is limited by the subendocardial blood flow in the ischaemic myocardium as described in other studies [35, 36].

After administration of 10^{-6} M DK, the coronary resistance was increased by 43 % in this study. It was significantly increased in our buffer-perfused hearts and remained unchanged in our blood-perfused hearts. In the present study, coronary blood flow per beat was considerably increased (+36 %) without pacing.

The relation between subendocardial and subepicardial flow remained nearly constant over the three experimental steps. This finding is in concert with our two preceding studies [13, 14]. From the previous studies and the present study on non-ischaemic myocardium, however, we cannot conclude whether bradycardia produces a selective increase in subendocardial blood flow in the ischaemic myocardium as described in other studies [35, 36].

Conclusion: The agent seems useful in the treatment of various heart diseases by improving myocardial energetic balance, and it seems of value in the operating theatre by decreasing unwanted tachycardia after cardiac surgery or by inducing bradycardia during coronary artery bypass procedures on the beating heart.

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References


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