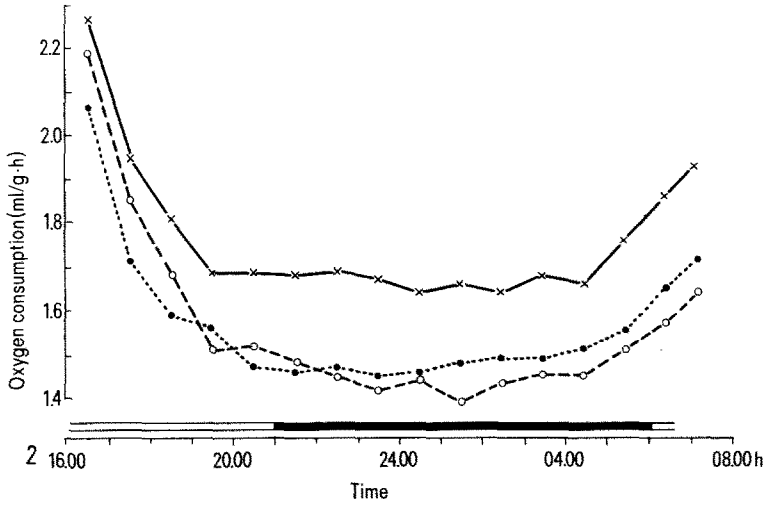

Fig. 2. Nocturnal oxygen consumption of different test-groups: × = normal males under long day conditions (n = 19), ● = castrated males under long day conditions (n = 12), ○ = castrates treated with Testoviron (n = 18). Each single value gives the respective hourly mean of all animals tested. The bar in black and white shows the LD-cycle under laboratory conditions.

highly significant higher body temperature (42.8±0.18 °C) than normal male quails; under short day conditions (testicles inactive), these differences do not occur. Both test groups show approximately equally high body temperatures (average values: males 43.1 °C, castrates 43.3 °C) above those measured under long day conditions. Through Testoviron or Testoviron-Depot, the body temperature of castrates held under long day conditions can be lowered to the level of control animals (active testes). Body temperature rises again, when the effect of the given preparation diminishes (figure 1).

2. Metabolism: All groups tested showed an oxygen consumption which figured approximately 35% above the expected value[5]. This supports Blem's results[6].

In relation to g b.wt, castrates' metabolism is reduced about 11% compared with that of the normal males (1.52±0.13 respectively 1.71±0.11 ml O_2/g·h; figure 2). This difference is highly significant.

The average weight of castrates (123 g) lies, however, approximately 7% above that of control animals (115 g). If this weight specific effect is taken into account, no difference between the metabolism of castrates and males can be seen. Compare also with Pohl[7] here.

During the time in which the testosterone preparation is effective (low body temperature), metabolism of the castrates does not change (before: 1.52±0.13; after: 1.51±0.07 ml O_2/g·h). Therefore, the changed body temperature is probably due to different thermal conductance (insulation), caused for example by an accumulation of reserve fat. Accordingly further experiments have been undertaken.

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Effects of isoproterenol and dopamine on the myocardial hexose monophosphate shunt[1]

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Summary. Long-term exposure of rats to isoproterenol and dopamine resulted in an increase of glucose-6-phosphate dehydrogenase activity and a greater availability of 5-phosphoribosyl-1-pyrophosphate in the myocardium. These results are interpreted to indicate an enhanced flow through the hexose monophosphate shunt.

The stimulatory effect of catecholamines on myocardial glycogenolysis is well established[3,4], their long-term influence on the hexose monophosphate shunt (HMS), however, has not yet been sufficiently elucidated. The HMS is important for cardiac metabolism mainly because it supplies ribose-5-phosphate for production of 5-phosphoribosyl-1-pyrophosphate (PRPP). This is an essential substrate necessary for the conversion of the purine bases adenine and hypoxanthine to the corresponding mononucleotides as well as for the biosynthesis of purine and pyrimidine nucleotides[5]. Therefore, the HMS was evaluated in rat hearts under the influence of isoproterenol and dopamine. Compared with other methods[6,7] our procedure for assessing the HMS is based on the in vitro-measurement of the activity of glucose-6-phosphate dehydrogenase (G-6-P-DH, EC 1.1.1.49), the first and rate-limiting enzyme of the HMS[8], and the in vivo-determination of the available PRPP, which is supplied by the HMS via ribose-5-phosphate.

Material and methods. All experiments were done on female Sprague-Dawley rats (200–220 g) fed a diet of Altromin® with free access to water. Isoproterenol (pur-

chased from C.H. Boehringer, Ingelheim) was s.c. injected in different doses (0.1, 1 and 25 mg/kg) either alone or in combination with the calcium-antagonistic compound D 600 (a gift from Knoll AG, Ludwigshafen) or with the β-receptor blocking agent atenolol® (generously supplied by ICI-Pharma, Heidelberg). Dopamine (kindly provided by Giulini Pharma, Hannover) was applied either s.c. in a high dose (500 mg/kg) or as constant i.v. infusion (1 mg/kg and 10 mg/kg/h in saline containing 0.01% ascorbic acid).

Table 1. Activity of myocardial glucose-6-phosphate dehydrogenase (units/g protein) after 24 h of exposure to different doses of isoproterenol s.c. applied either alone or in combination with compound D 600 or atenolol®

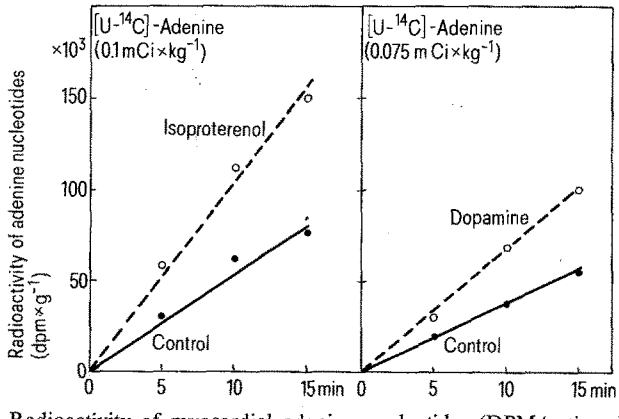
	n	Units/g protein
Control	28	4.3±0.15
Isoproterenol		
0.1 mg/kg	7	6.6±0.35*
1 mg/kg	8	11.4±0.72*
25 mg/kg	5	10.8±1.23*
Isoproterenol (25 mg/kg)		
+ compound D 600	9	6.6±0.25*
Isoproterenol (1 mg/kg)		
+ atenolol®	8	5.0±0.22**

D 600 was injected twice (10 and 5 mg/kg s.c. 12 h apart). Atenolol® was also given twice (1 mg/kg s.c. 12 h apart). Mean values ±SEM, n = number of experiments. *$p < 0.0005$, **$p < 0.025$ compared with the control value.

Table 2. Effect of dopamine administered s.c. as a single dose or as constant i.v. infusion on the activity of glucose-6-phosphate dehydrogenase (units/g protein)

	n	Units/g protein
Control	14	4.5±0.17
Dopamine		
S.c. injection of 500 mg/kg	8	10.3±0.80*
Constant infusion of 1 mg/kg/h	5	5.7±0.25**
Constant infusion of 10 mg/kg/h	9	8.3±0.54*

All measurements were done after 48 h. The infusion rate of dopamine was 5 ml/kg/h. Control values were obtained in hearts of rats which had received a constant i.v. infusion of 0.9% NaCl containing 0.01% ascorbic acid. Mean values ±SEM, n = number of experiments. *$p < 0.0005$, **$p < 0.0025$.



Radioactivity of myocardial adenine nucleotides (DPM/g tissue) after different periods of exposure to i.v. injected [U-^{14}C]-adenine (10 mg/kg in 0.9% NaCl) under control conditions (closed circles), 24 h after s.c. application of 25 mg isoproterenol/kg (open circles in left hand panel) and after 48 h of constant i.v. infusion of 10 mg dopamine/kg.h (open circles in right hand panel). Each point represents the mean of 2 experiments.

In order to perform i.v. infusion, a steriflex catheter (Code I63-IO, Vygon Company, Aachen) was inserted into the right jugular vein of the rats anesthetized with ether. It was s.c. directed towards the neck, fixed there and connected to a 20 ml syringe which was placed in an infusion pump (Type 5003, Infors AG, Hofstetten bei Basel). The animals could then move around freely in their cages. The infusion rate was 5 ml/kg/h. To prepare the hearts for measuring G-6-P-DH activity, a cannula was placed in the ascending aorta after thoracotomy and tightly fixed with a thread. The hearts were rapidly excised, and the coronary arteries were perfused via the cannula with an ice-cold KCl-solution (0.15 M containing 8 ml of 0.02 M $KHCO_3$/l) in order to remove blood and to stop beating.

Homogenization of the hearts in the perfusion medium, centrifugation, dialysis of the supernatants and measurements of G-6-P-DH activity were done according to the methods of Glock and McLean[9,10]. Protein concentration in the dialysate was determined using the modified biuret reaction[11]. The specific activity of G-6-P-DH was expressed as units/g protein. The available pool of PRPP was assessed from the radioactivity of adenine nucleotides after different periods of in vivo-exposure to i.v. administered [U-^{14}C]-adenine (specific activity 282 mCi/mmole, 0.1 or 0.075 mCi/kg, concentration of adenine 10 mg/kg)[12].

Results and discussion. The data in table 1 show that the activity of G-6-P-DH was enhanced 24 h after s.c. administration of different doses of isoproterenol. A similar increase in G-6-P-DH activity was observed in rats hearts during development of hypertrophy induced by aortic constriction[13] and in the unaffected part of the myocardium after coronary artery ligation[14]. Compound D 600[15] attenuated and atenolol® almost completely prevented the isoproterenol-induced stimulation of G-6-P-DH activity. This result demonstrates that the effect of isoproterenol is most probably due to stimulation of cardiac β-receptors. The data obtained in experiments with dopamine are summarized in table 2: 48 h after s.c. injection of a single high dose, as well as after 48 h of constant i.v. infusion of low doses of dopamine, the activity of cardiac G-6-P-DH was found to be also increased. As shown in the figure, the in vivo-incorporation of ^{14}C-adenine into myocardial adenine nucleotides was enhanced both after application of a single dose of isoproterenol and after constant infusion of dopamine indicating a greater availability of PRPP.

From the increased activity of G-6-P-DH and the greater availability of PRPP observed after long-term exposure to isoproterenol and dopamine, it can be concluded that the flow through the HMS is actually enhanced under these conditions. In this context it is interesting to note that adenine nucleotide biosynthesis is also enhanced in isoproterenol-stimulated hearts[16]. It may thus be suggested that an increased flow through the HMS contributes significantly to the enhancement of adenine nucleotide synthesis. Furthermore, our studies with dopamine provide some new aspects concerning the clinical use of this sympathomimetic compound for the treatment of certain kinds of cardiac insufficiency and shock[17].

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Baroreceptor function changed by breathing

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Summary. The efferent sympathetic activity (ESA) of the carotid nerve is related to breathing, and can be driven by stimulation of the latter, e.g. by airway occlusion. The ESA controls both carotid wall stiffness and the excitability of nervous receptor elements. Therefore, breathing is capable of changing the carotid baroreceptor function.

Events of efferent control alter the receptor function as was shown for different sense organs[2]. In contrast, receptors involved in visceral systems have not often been investigated to date. Receptors important for blood pressure regulation are generally formed as mechanoreceptors[3], i.e. the intravasal pressure as the adequate stimulus does not affect the nervous receptor elements directly, since the vessel wall is interposed as a stimulus transformer. Above all the blood pressure rise stretches the vessel wall and this in turn alters the geometrical arrangement of nervous receptor elements located in the outer part of vessel wall. The receptor elements respond in terms of a change in their membrane potential and, provided their critical threshold is exceeded, action potentials will be generated.

Therefore, baroreceptor function could be influenced by efferent control in 2 different ways:

a) By changing the vessel wall stiffness; in this case the transformation of the blood pressure into the utilized stimulus affecting the nervous receptor elements is shifted.

b) By changing the excitability of nervous receptor elements. In the latter case, the formation of receptor potential and/or action potentials is altered.

The efferent control of baroreceptors could be mediated by efferent sympathetic activity (ESA) that influences both the vessel wall stiffness[4] and the excitability of nervous receptor elements[5-7].

On the other hand, the ESA is altered by breathing, this fact being well-known and generally accepted. Consequently, it can be supposed that breathing is capable of changing the sensitivity of baroreceptors. In order to test this assumption, experiments were done using the carotid baroreceptors in dogs because this region is easily accessible. The carotid bifurcation is innervated by the efferent fibres of the carotid nerve (CN) sometimes called ganglioglomerular branch. These fibres are routed separately from the carotid sinus nerve (CSN) that leads the baroreceptor afferents to the brain stem. The CN originates in the sympathetic superior cervical ganglia and terminates with a larger part of its fibres directly in the carotid wall[8] forming a terminal network[9].

The quantity of ESA led by the CN is related to the respiration cycle[10]. The influence of breathing upon this quantity can be demonstrated distinctly by mechanical occlusion of the airway. During occlusion, the efferent activity increases simultaneously in both the phrenic nerve and the CN (figure 1).

The influence of the increased ESA induced by airway occlusion upon the wall stiffness in the carotid bifurcation

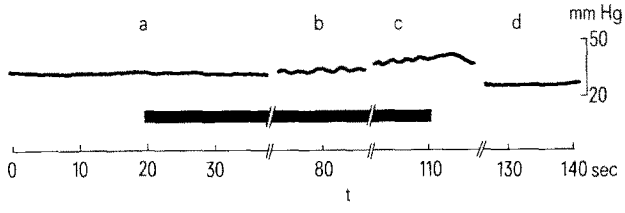

Fig. 2. Rise of perfusion pressure in an isolated carotid bifurcation caused by airway occlusion (line indicates occlusion period).

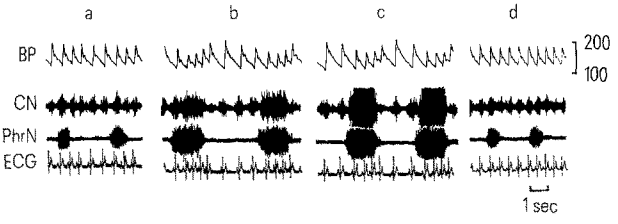

Fig. 1. Increasing efferent activity in both carotid nerve (CN) and phrenic nerve (PhrN) induced by airway occlusion. a and d: control before and after occlusion; b and c: 20 and 60 sec after starting occlusion, respectively; blood pressure (BP) was measured in a lingual artery.

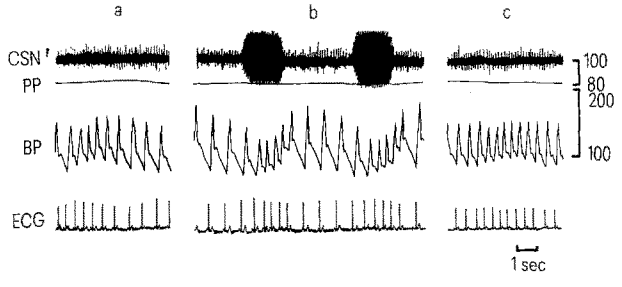

Fig. 3. Spontaneous burst of mass discharges in the neurogram of afferent carotid sinus nerve (CSN) during airway occlusion. The isolated carotid bifurcation was perfused constantly in order to keep the perfusion pressure (PP) at the same level. a and c: control before and after occlusion; c: 20 sec after starting occlusion; blood pressure (BP) was measured in the opposite lingual artery.