Transmural Pressure as a Determinant of Basic Intrinsic Heart Rate

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Summary. It was observed that the heart rate was minimum at zero transmural pressure. The mean heart rate at zero transmural pressure was 23 ± 5/min. This mean heart rate increased from 23 ± 5/min to a peak value of 40 ± 6/min (74% acceleration) when the transmural pressure was raised from 0 to +4 mm Hg and to a similar peak value of 36 ± 8/min (56% acceleration) when the transmural pressure was lowered from 0 to −4 mm Hg. The peak values attained at ± 4 mm Hg were highly significant ($p < 0.001$). It is concluded that the heart rate at zero transmural pressure represents the basic intrinsic pacemaker frequency independent of neural, humoral, thermal and haemodynamically induced mechanical influences.

Changes in the chronotropic response of the heart through mechanical stretch induced by changing the intracardiac pressure in isolated amphibian (PATHAK[1,2]), and mammalian (PATHAK[3]) hearts have been reported. Mechanical stretch has been shown to be a fundamental stimulus for pacemaker activity (PATHAK[4]). These studies led to the establishment of the concept of intrinsic autoregulation of heart rate through changes in the pacemaker stretch (PATHAK[5,6]). Recently extracardiac pressure changes induced through pericardial distension have also been shown to alter the pacemaker response (PATHAK, JOG and GOYAL[7]). In view of the involvement of the pacemaker by both intracardiac and extracardiac mechanical stretch, it was considered useful to study the relationship between transmural pressure and heart rate.

Material and methods. Hearts of pithed or decapitated frogs were perfused in situ with frog Ringer's solution (NaCl, 102 mM; KCl, 1 mM; $CaCl_2$, 1 mM; $NaHCO_3$ 1 mM; pH 7.6). The vagosympathetic trunks were cut as an additional precaution. A needle or polythene catheter was implanted in the intact pericardial cavity. The intracardiac (intrasinus) pressure was altered by changing the perfusion pressure. The extracardiac (pericardial) pressure was altered by injecting or withdrawing Ringer's fluid. Due to the mutual interaction between the intrasinus and extrasinus pressures, the resultant transmural (intrasinus-pericardial) pressure was of small magnitude when only one of them was altered. To induce larger changes in the transmural pressure, the two pressures were altered in opposite directions, i.e. while the perfusion pressure was raised, the pericardial pressure was reduced or vice versa. All pressures were monitored with the help of an electronic pressure meter through a statham pressure transducer. The level of the sinus venosus (the pacemaking chamber in frog heart) was fixed as the common 'zero reference' for all pressure recordings. The heart rate was monitored on a rate meter triggered by the ventricular complex of the electrocardiogram (ECG). The ECG and pericardial pressure were recorded on two channels of an electronic recorder. Details of experimental set-up are shown in Figure 1. The entire system was thoroughly checked several times during each experiment for any possible leak.

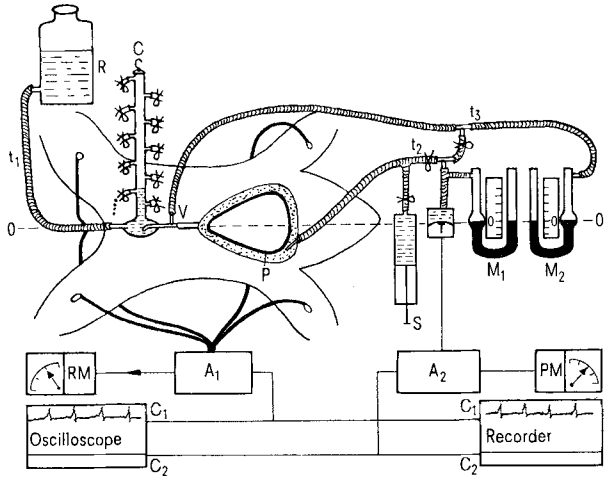

Fig. 1. Block diagram of the experimental set-up. A_1, ECG and A_2, pressure amplifiers. C, specially designed perfusion cannula with overflow outlets at 1 cm intervals. The curvature in the outflow limb of the bulb of the cannula controlled the velocity of fluid inflow into V, the posterior venacava. C_1, C_2, the 2 channels of oscilloscope and recorder. M_1, M_2, reservoir type Hg-manometers in parallel with the transducer, T and pressure meter, PM to match their responses exactly within 0.25 mm Hg. M_1 and M_2 monitored the average pericardial and sinus pressures. P, pericardial cavity; R, Ringer reservoir; RM, heart rate meter; S, syringe for injecting and withdrawing fluid from the pericardium; t_1, t_2 and t_3 plastic connecting tubing. The sinus venosus was the common reference 0 level as indicated by the interrupted horizontal line.

The frog being a poikilothermic animal, warming of the perfusion fluid was not necessary. The experiments were conducted at laboratory temperature (around 20 °C). There was no potential heat exchanger around the perfusion assembly. The probe of a sensitive electronic thermometer was inserted in the connecting tube (Figure 1, t_3) near the heart and the temperature of the perfusion fluid was continuously monitored and remained constant during the experiment. The fluid used for pericardial distension was withdrawn from within the perfusion system into the syringe (Figure 1, t_2). Hence the fluid which entered the heart and which distended the pericardium had the same temperature and chemical composition.

Results. The difference between the perfusion (intracardiac) and pericardial (extracardiac) pressures represented the transmural pressure. The transmural pressure was positive when the intracardiac pressure exceeded the extracardiac pressure, while it was negative when the extracardiac pressure exceeded the intracardiac pressure. The transmural pressure was varied in graded steps from +8 to −14 mm Hg and the resultant changes in the heart rate were investigated in 20 isolated perfused frog hearts.

Figure 2 illustrates the changes in the heart rate on first trial with change in the transmural pressure in 8 different hearts. In 4 hearts (left side) the effect of negative

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Heart rates at different transmural pressures

Out of 20 hearts	Transmural pressures in mm Hg											
	+8	+6	+4	+2	0	−2	−4	−6	−8	−10	−12	−14
Mean heart rate	30	36	40	36	23	34	36	35	32	29	27	25
Acceleration of mean rate at 0 transmural pressure (%)	30	56	74	56	0	48	56	52	39	26	17	9
Standard deviation	–	–	6.0	–	5.1	–	8.8	–	–	–	–	–
Standard error	–	–	1.6	–	1.2	–	2.2	–	–	–	–	–
't-value	–	–	8.8	–	–	–	5.6	–	–	–	–	–
Probability (p)	–	–	0.001	–	–	–	0.001	–	–	–	–	–

transmural pressure is shown, while in the other 4 hearts (right side) the effect of both positive and negative transmural pressure is shown. The heart rate was minimum at 0 transmural pressure achieved by equalizing the intracardiac and extracardiac pressure. When the transmural pressure was changed from the zero level, the heart accelerated to attain a peak rate followed by deceleration both at positive as well as at negative transmural pressure. Occasionally, due to severe bradycardia at high transmural pressures (± 10 to ± 14 mm Hg), the heart rate reached a value lower than that at the zero transmural pressure (Figure 2, top right). Since these transmural pressures were very much outside the physiological limits, the lower values of heart rates in such cases cannot be regarded as natural minimum rates. The expected physiological limits of transmural pressure range is 0 to ± 4 mm Hg. Within this range of transmural pressure, the minimum heart rate was at 0 transmural pressure and acceleration to a peak occurred on changing the transmural pressure to ± 4 mm Hg in all the 20 hearts.

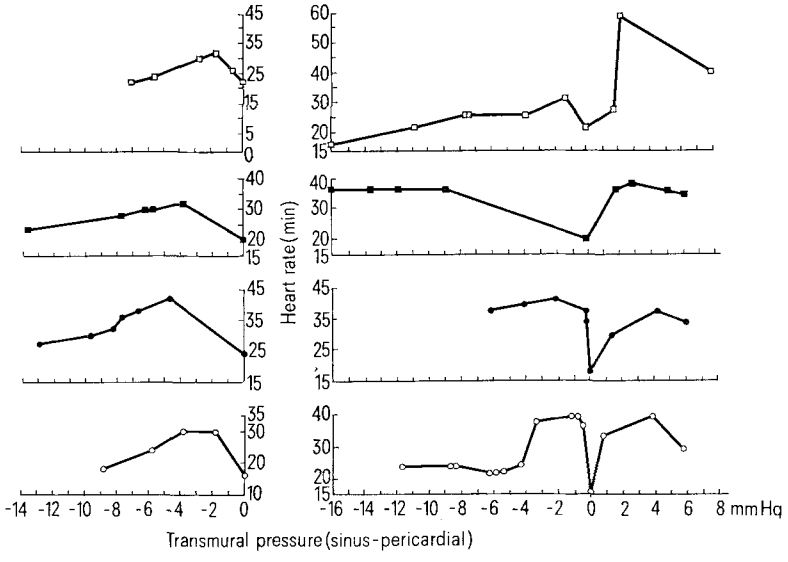

Fig. 2. Rate changes in 8 hearts on first distension trials. Leftside, 4 hearts showing the effect of negative transmural pressures. Rightside, another 4 hearts showing the effect of both positive and negative transmural pressures. The heart rate was minimum at zero transmural pressure (except in the heart shown on top right, see text) and increased to a peak as the transmural pressure was changed to positive or negative values.

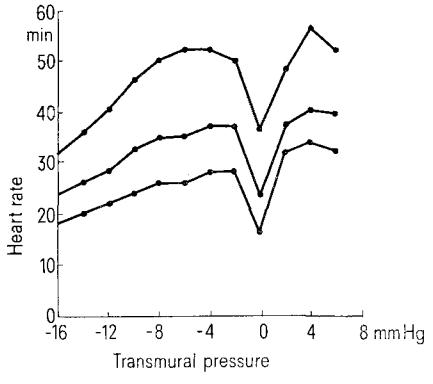

Fig. 3. Variations in mean heart rate at different transmural pressures is represented by the middle curve. The upper and lower curves represent the extreme ranges of heart rate changes observed in some trials.

Two or three trials, as shown in Figure 2, were conducted in each heart and the average values of heart rates at different transmural pressures were calculated for each heart. The mean values of heart rates derived from these average values of the 20 hearts along with statistical analysis of the data are presented in the Table. It is seen that the mean minimum heart rate at 0 transmural pressure was 23 ± 5/min. It increased to the peak value of 40 ± 6/min (74% acceleration) when the transmural pressure was changed from 0 to +4 mm Hg and to 36 ± 8/min (56% acceleration) when the transmural pressure was changed from 0 to −4 mm Hg. The peak values at +4 and −4 mm Hg transmural pressures were statistically highly significant ($p \leq 0.001$). Figure 3 shows the pattern of change in the mean heart rate (middle curve) along with the maximum and minimum limits of variation in rates observed with changes in the transmural pressure in the 20 hearts.

The values of heart rate recorded from the monitoring rate meter were rechecked from the sinus complexes of the ECG. These values, therefore, represent the pacemaker frequency.

Discussion. In the isolated denervated hearts, extrinsic neurohumoral influences are absent. Any possible thermal or chemical effect was also ruled out because the perfusing and distending solutions had the same temperature and chemical composition. Further the rate changes only occurred during change in the pressure without any other variable being involved, and the rate changes were quite reversible on reversing the pressure change. Therefore, the observed chronotropic changes due to alterations in the transmural pressure could only be attributed to changes in the pacemaker activity in response to pressure-induced mechanical effect.

The present results are quite consistent with the previous observations on pacemaker response to mechanical stretch (PATHAK[1-4]; PATHAK, JOG and GOYAL[7]). In previous approaches to the assessment of basic intrinsic heart rate (JOSE and COLLISON[8]), the role of pressure-induced mechanical stretch was not appreciated. The present work establishes that the true basic intrinsic heart rate can only be obtained when, besides eliminating the extrinsic neurohumoral and thermal influences, the effect of pressure induced stretch is also excluded. The minimum heart rate at 0 transmural pressure, therefore, represents the true basic intrinsic pacemaker frequency. It is also clear that the transmural pressure is an important determinant of basic intrinsic heart rate.

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Rudiments of an Ability for Time Measurement in the Cavernicolous Fish *Anoptichthys jordani* Hubbs and Innes (Pisces Characidae)

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Summary. Rudiments of an ability for endogenous time-measuring are indicated a) by bimodal activity in the dark phase of LD-cycles of 16:16 or 24:24 h and b) by damped activity oscillations frequently following a transition from LD to constant conditions. These oscillations always have the same period length as the applied LD.

One may expect that the circadian rhythm depending on the integrity of many genes does not disappear suddenly but degenerates gradually during the regressive evolution under cave conditions. The knowledge of these degeneration steps may allow conclusions on genetics and physiology of the intact endogenous clock. The cavernicolous fish *Anoptichthys jordani* is a suitable object for such investigations, because it is genetically connected by intermediate forms with its surface ancestor *Astyanax mexicanus*[1]. This work is concerned with investigations of an endogenous stochastic control and of rudiments of an endogenous rhythm of swimming activity in 4 specimens (3 ♂♂, 1 ♀) of the blind extreme cavernicolous form.

Methods. The swimming activity was recorded by infrared beams fixed 2–3 cm below the water surface (in some experiments an additional beam near the bottom). The measuring interval was 30 min. The animals were isolated from each other during the experiments. According to the length of the artificial light period, the LD experiments lasted 215–606 h. The DD and LL experiments lasted 304–316 h. The series of data were investigated with regard to periodic distributions by a periodogram analysis program[2] in the computer-centre of the University of Münster, and with regard to stochastic distributions of activity by the methods applied by LEHMAN et al.[3].

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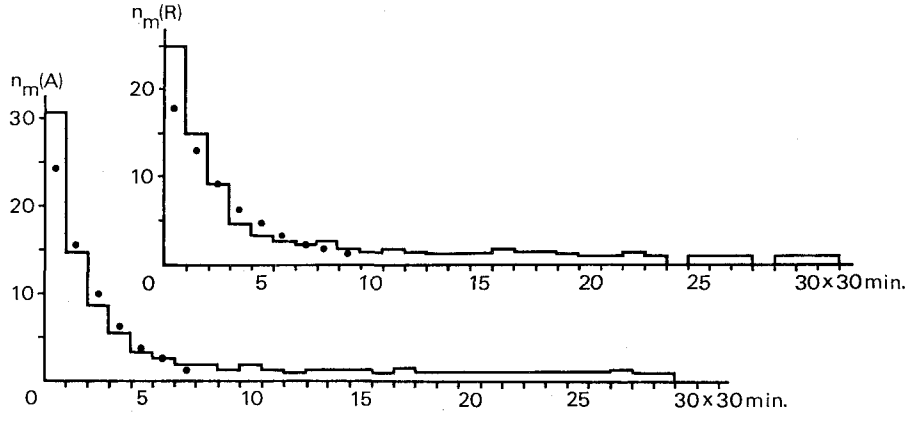

Fig. 1. Geometric means of frequency histograms of A and R from 20 DD experiments. Ordinate: means of the observed values. Points: fitted exponential function in the range of agreement including 71% of the A- and 70% of the R-values (χ^2-test, $p_A = 0.88$, $p_R = 0.75$. $f_A = -0.48$, $f_R = -0.34$).