7. D. Penaloza and F. Sime, Bull. Physiol-Pathol. Resp., 4, p. 17 and Discussions, p. 42 (1968).
8. R. Sujoy et al., Br. Heart J., 31, 52 (1969).

INOTROPIC EFFECT OF RHYTHM DISPERSION

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UDC 612.172.2

KEY WORDS: isometric contraction; rhythm variance; chronotropic and inotropic effects.

Dependence of the force (and other parameters) of contractions on the frequency of stimulation (chronotropic and inotropic effects) is an important characteristic of the myocardium which enables it to change its contractility rapidly from cycle to cycle [2, 5]. The type of relationship between frequency and steady-state force in the myocardium of warm- and cold-blooded animals has been shown to be essentially nonlinear [3, 4]. Chronotropic and inotropic effects of the myocardium are manifested not only in the steady-state frequency–force relationship, but also in the dependence of force on interstimulus interval, in the form of such well-known phenomena as the extrasystolic reduction in force and its postextrasystolic potentiation. Dependence of the force of contractions on the extrasystolic and postextrasystolic intervals likewise is essentially nonlinear. In such a nonlinear system, the actual character of the interstimulus sequence may exert an additional effect, manifested as an increase or decrease in the force of contractions. If the stimulus sequence is a random process, as is the case in arrhythmias, the mean force of contractions in a fixed time interval may depend on several statistics of the interstimulus sequence: not only, moreover, on the mean value (which is trivial), but also on the second and third statistical moments (variance, asymmetry), and autocorrelation. Dependence of the force of contractions on rhythm dispersion is of definite practical interest, for the heart under natural conditions (and even more, in pathological arrhythmias) works under random conditions [1]. Moreover, investigation of the statistical features of stochastic distributions of R-R intervals on the ECG in some extremal situations and during physiological and pathological arrhythmias has shown that the statistics of the rhythm are highly sensitive to changes in autonomic regulation [1].

The aim of this investigation was an experimental study of the inotropic effects of rhythm dispersion.

EXPERIMENTAL METHOD

Experiments were carried out on papillary muscles and trabeculae of rabbit and rat atria. Contractions were recorded under isometric conditions. The composition of the basic solution and other technical details were described previously [2]. The preparations were first stimulated at constant frequency (determined rhythm). A random gaussian uncorrelated sequence of pulses of the same mean frequency, but with controllable dispersion, was then applied from a special generator. The coefficient of variation of the rhythm CV_T, equal to $\sigma_T/\overline{T}$ (where σ_T is the standard deviation of interpulse intervals, $\overline{T}$ the mean interpulse interval) was assigned between 8 and 40%. After a random realization had been recorded with between 100 and 200 cycles, a return was made to a steady rhythm. Only those realizations in which the force of contractions before and after application of the random rhythm remained constant were used in the calculations (realizations with time drift were excluded).

Laboratory of Biophysics, Sverdlovsk Research Institute of Work Hygiene and Occupational Diseases. Laboratory of Regulation of the Heart and Coronary Circulation, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR I. K. Shkhvatsabaya.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 94, No. 8, pp. 20-22, August, 1982. Original article submitted March 16, 1982.

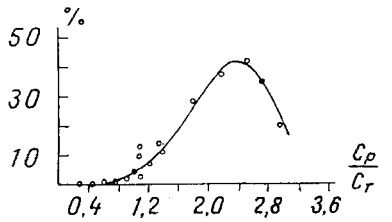

Fig. 1. Increase in force of contractions under random conditions compared with that determined as a function of steepness of force–frequency characteristic curve. Force–frequency characteristic curve estimated in accordance with the relationship C_P/C_T ($C_P = \sigma_P/\overline{P}$, $C_T = \sigma_T/\overline{T}$), where σ_P, σ_T represents the standard deviation of force σ_P and of interpulse intervals σ_T; $\overline{P}$, $\overline{T}$, the mean values of force at interpulse intervals. Abscissa, parameter of "variability" of amplitudes of contractions, equal to ratio of coefficient of variation of force to coefficient of variation of interpulse intervals; ordinate, relative to increase in force.

The force of contractions during the determined rhythm was compared with the mean force under random conditions. For each random series of values of force (and sometimes the derivative of force) the mean value of the force, dispersion, and coefficient of variation of force were calculated. In another series of experiments, the pressure was recorded through a balloon introduced into the ventricle of the dog's heart. The heart was perfused from a donor dog. In experiments on the intact heart, the frequency of stimulation from the random pulse generator was above natural.

EXPERIMENTAL RESULTS

In more than half of the preparations of rabbit ventricles, the inotropic effect of rhythm dispersion (coefficient of variation of the rhythm from 0.4) was not more than a few per cent. However, in such cases the steepness of the force–frequency curve was low. In preparations with a steep force–rhythm curve the effect of dispersion of the interpulse intervals was to increase the mean force of contractions by up to 40% compared with the determined rhythm. One such case is illustrated in Fig. 1. The use of a dimensionless parameter of "variability" of the amplitudes of contractions (equal to the ratio of the coefficient of variation of the force to the coefficient of variation of interpulse intervals) is due to the fact that the inotropic effect of rhythm dispersion is a function simultaneously both of the mean frequency of stimulation and of the rhythm dispersion itself. With a constant frequency of stimulation, the greater the scatter of values of interpulse intervals, the greater the positive inotropic effect of dispersion. With an increase in the mean frequency, with the shift into the region of a steeper force–frequency curve, the positive inotropic effect of rhythm dispersion increases. It will be clear from Fig. 1 that the inotropic effect of rhythm dispersion is an extremal function of both frequency and dispersion. Of the factors which increase the inotropic effect of rhythm dispersion, a rise of temperature and a fall in the extracellular calcium concentration may be noted. Addition of adrenalin (10^{-6} g/ml) or a change from isometric to isotonic conditions reduces the inotropic effect of dispersion. If instead of the force of contractions, its derivative $\dot{P}_{max}$ is taken as the parameter of contractility, the effect of rhythm dispersion becomes clearer still. With identical statistics of interpulse intervals, the effect of rhythm dispersion for $\dot{P}_{max}$ was approximately 1.5 times greater than for the amplitude of contractions.

No positive inotropic effect of rhythm dispersion could be observed in the rat heart. The inotropic effect of rhythm dispersion in the rabbit atria, moreover, was much less marked than in the ventricles. Inotropic effects of dispersion differed sharply in the rabbit papillary muscle and the intact dog's heart. In isovolumic dogs' hearts an increase in rhythm dispersion led to a fall of pressure of between 5 and 30%. This was accompanied by a decrease in the oxygen consumption of the heart and a decrease in the coronary blood flow by between 10 and 15%.

When the force–frequency characteristic curve is steep, rhythm dispersion itself has a positive inotropic effect in the rabbit ventricle. The additional activation thus arising may be from 30 to 40%. The inotropic effect of rhythm dispersion in the region of frequencies of stimulation of 0.33-1.0 Hz increases with an increase in frequency, and at a given frequency it depends on dispersion of the interpulse intervals.

Unfortunately, experiments on strips of myocardium do not allow the investigation to be undertaken at high frequencies (over 1.0 Hz) because of the developing hypoxia and irreversible injury to contractility. In intact hearts, in the region of frequencies of 2-3 Hz, rhythm dispersion leads to a negative and not a positive inotropic effect. It is therefore difficult to compare results obtained on strips of myocardium and the intact heart. These results can be understood by the use of a simple model of chronotropic and inotropic effects. In the simplest case, these effects in the heart of warm-blooded animals can be described by a function of the type

$$P_n = A\left(1 - e^{-\alpha T_n}\right) e^{-\beta T_{n-1}}, \tag{1}$$

where P_n is the force of any contraction, T_n, T_{n-1} the interpulse intervals, and A, α, and β are constants, such that $\alpha > \beta$. It can be shown that the mathematical expectancy of force (i.e., the mean value of the force of contractions $\overline{P}$ in a random gaussian sequence with mean interpulse interval $\overline{T}$ and with dispersion D_T) is

$$\overline{P} = A\left(1 - e^{-\alpha\overline{T}} \cdot e^{\frac{\alpha^2}{2} D_T}\right) e^{-\beta\overline{T}} \cdot e^{\frac{\beta^2}{2} D_T}. \tag{2}$$

The relative change of force (relative to force P_{det}, where P_{det} is the force of contractions at the determined rhythm, i.e., $T_n = \overline{T}$ and dispersion $D_T = 0$) is given by

$$\overline{P}/P_{det} = \frac{e^{\frac{\beta^2}{2} D_T}\left(1 - e^{-\alpha\overline{T}} \cdot e^{\frac{\alpha^2}{2} D_T}\right)}{1 - e^{-\alpha T}}. \tag{3}$$

It follows from equation (3) that at high frequencies, we can expect that $\overline{P}/P_{det} < 1$, and that at low frequencies $\overline{P}/P_{det} > 1$. Of course, the possibility cannot be ruled out that in the intact heart additional factors may be present which can reduce the force of contractions in arrhythmias (a decrease in the coronary blood flow, for example).

LITERATURE CITED

1. A. D. Voskresenskii and M. D. Ventul', in: Problems in Space Biology [in Russian], Vol. 26, Moscow (1974), p. 175.
2. V. A. Izakov, G. P. Itkin, V. S. Markhasin, et al., in: Biomechanics of Heart Muscle [in Russian], Moscow (1981), p. 180.
3. E. A. Johnson, in: Handbook of Physiology. The Cardiovascular System, Vol. 1, Washington (1979), p. 475.
4. J. Koch-Weser, Am. J. Physiol. 204, 451 (1963).
5. J. Koch-Weser, and J. R. Blinks, Pharmacol. Rev., 15, 601 (1963).