The Possible Role of Intracellular Ca^{2+}-Stores in the Rhythm-Inotropic Relationship of Frog Heart Muscle (A Simulation Study)

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Abstract. The hypothesis that intracellular calcium stores play an essential role in determining force-frequency relationships of frog myocardium was tested quantitatively. A simplified mathematical model of excitation-contraction coupling in frog heart muscle was developed and its behaviour under various patterns of stimulation was analysed by means of computer simulation. The model represents a system of ordinary differential equations for individual fluxes within the cell Ca^{2+}-recirculation system and includes a one-compartmental intracellular pool as opposed to the two-compartmental structure of the mammalian sarcoplasmic reticulum (Kaufmann et al. 1974). The behaviour of the model is consistent with available experimental data concerning the basic rhythm-inotropic characteristics of amphibian myocardium and offers some evidence in favour of the basic concept. Within the framework of the proposed model the staircase phenomena in amphibia were accounted for and the impact of different intracellular Ca-movements on the resulting contractile response and rhythm-inotropic phenomena was elucidated.

Key words: Excitation-contraction coupling — Frog myocardium — Simulation

Introduction

Currently it is widely accepted that the contractile activity of myocardial cells of cold-blooded and warm-blooded animals depends on the mode of excitation (Meijler 1962; Koch-Weser and Blinks 1963; Chapman and Niedergerke 1970; Morad and Goldman 1973; Khodorov et al. 1977; Shultze 1981; Wendt-Gallitelli and Jacob 1982).

During each excitation the influx of Ca^{2+} to the myoplasm of mammalian cardiomyocytes occurs mainly from two sources: the sarcoplasmic reticulum (SR) and the extracellular medium (Horackova 1984). The dependence of contractile force on stimulation frequency, or rhythm-inotropic relations (RIR), is accounted for by an involvement of the SR in controlling Ca^{2+} concentration in the region of

the contractile apparatus (Nayler and Dresel 1984), namely by the ability of SR to rapidly sequester and release Ca^{2+} ions during each contractile cycle (Winegrad 1982).

In the amphibian myocardium SR is poorly developed (Page and Niedergerke 1972), so most investigators try to attribute an increase in contractile force of the frog myocardium with stimulation frequency (the Bowditch staircase) to augmentation of Ca^{2+} influx via either voltage-operated Ca channels (Chesnais et al. 1978; Noble and Shimoni 1981) or/and potential dependent Na-Ca exchange diffusion (Langer 1983). Some authors, however, believe that in amphibian myocardium, as well as in mammals, the RIR are mainly due to the intracellular calcium stores (Niedergerke 1956; Khodorov et al. 1977; Kitaigorodskaya et al. 1981).

It is worth mentioning that at present the relative contributions of each of the above-mentioned transfer mechanisms to the force-frequency relationship in frog myocardium cannot be exactly quantified from experimental data (Horackova 1984). The aim of the present study was to determine, using a mathematical model, whether the basic RIR in amphibian myocardium could be explained by assuming that the intracellular Ca-stores play a key role in the control of myoplasmic Ca^{2+} ion concentration. Hence, i) the beat-to-beat variation of inward Ca-current, and ii) Na^+ ions accumulation in the myoplasm during repetitive contractions, were both neglected. We present here a simple mathematical model for excitation-contraction coupling (ECC) in frog myocardium, which represents a modification of an existing ECC model for warm-blooded heart muscle (Kaufmann et al. 1974). Preliminary results of this investigation have been reported elsewhere (Mukumov et al. 1978; Pratusevitch et al. 1982).

Modification of an ECC model for myocardium of warm-blooded species

Kaufmann et al. (1974) developed a model for Ca^{2+} balance in the myocardial cell, which represented a generalization of the evidence presently available concerning the role of calcium in ECC in warm-blooded species (for a review, see Bassingthwaighte and Reuter 1972). Later on more sophisticated models of this kind were presented by Wong (1981) and Markhasin et al. (1985). A diagram of Ca^{2+} recirculation in the model by Kaufmann et al. (1974) is shown in Fig. 1*A*. The model takes into account the exchange of Ca^{2+} ions between the extracellular medium, the myoplasm and the mitochondria. In this figure the basic Ca^{2+} movements into and out of the myocardial cell are depicted along with their respective rate constants, according to Kaufmann et al. (1974): stationary Ca^{2+} influx (k_0), potential-dependent Ca^{2+} influx to the myoplasm (k_1); Ca^{2+} uptake by the longitudinal SR (k_2), potential-dependent Ca^{2+} translocation to the terminal cisternae (k_3), Ca-induced Ca-release from the cisternae (k_4) during excitation;

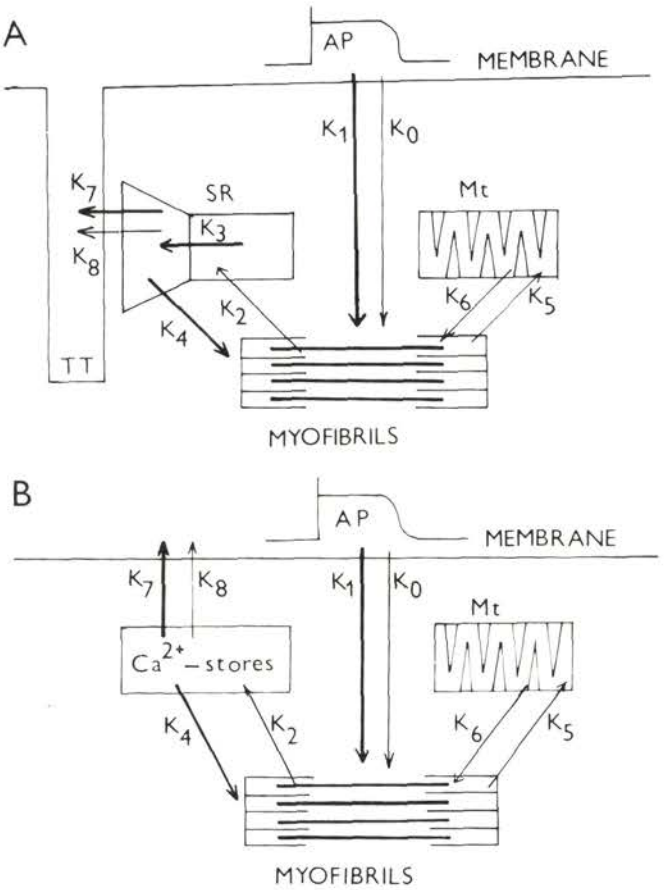

Fig. 1. Schemes for Ca^{2+} recirculation in the cardiac muscle cell: *A*) in the model of Kaufmann et al. (1974) for myocardium of the warm-blooded; *B*) in model (1) for ECC in the frog myocardium. Thick arrows indicate potential-dependent Ca^{2+} fluxes, thin arrows stand for the stationary ones. For further explanation, see text.

exchange of Ca^{2+} ions with mitochondria (k_5 and k_6); potential-dependent and stationary components of Ca^{2+} outward flux from the myocardial cell into its environment (k_7 and k_8).

The equation system of the model considered allowed to describe satisfactorily the main RIR characteristic of cat papillary muscle, namely the two-phase nature of contraction staircase upon the resumption of rhythmical stimulation of the heart muscle after a long rest interval and the effect of poststimulation potentiation (PSP) of contractions. These phenomena also are typical of the myocardium of

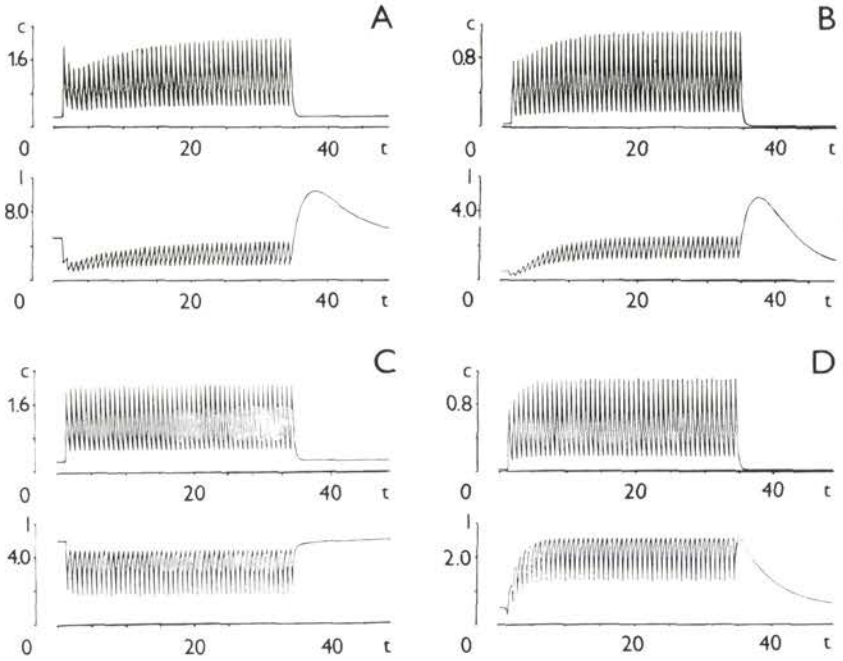

Fig. 2. The staircase phenomenon in the model of Kaufmann et al. (1974): The contribution of coefficients k_0 and k_3. Periodic stimulation (frequency 1.43 Hz, AP duration 0.2 s) after a long rest is simulated. The upper curves show variation of calcium content in the myoplasm (c), the lower curves show calcium content in terminal cisternae (l) of SR (both expressed in relative dimensionless units). The abscissa is time (t) in seconds. The coefficient values are as follow: (in s^{-1}): $k_1 = 5$, $k_2 = 4$, $k_4 = 2$, $k_5 = 0$, $k_6 = 0.1$, $k_7 = 2$, $k_8 = 0.2$ and *A*) $k_0 = 1$, $k_3 = 0.5$; *B*) $k_0 = 0.1$, $k_3 = 0.5$; *C*) $k_0 = 1$, $k_3 = 100$; *D*) $k_0 = 0.1$, $k_3 = 100$.

Constants $e = s = 1$; Functions $\alpha = \beta = \gamma = \text{sign}\,\frac{E_m + |E_m|}{2}$, $\beta = 1 - \alpha$ (cf. Fig. 3 in Kaufmann et al. 1974). Here E_m is the transmembrane potential. For the sake of simplicity the action potential (AP) in our calculations was represented by square-wave pulses of constant duration and amplitude.

some other warm-blooded animals (cf. Braveny and Kruta 1958; Koch-Weser and Blinks 1963; Khodorov et al. 1976).

In contrast to mammals, in amphibian myocardium the typical staircase response follows a steadily ascending pattern: during repetitive stimulation turned on after a long period of rest the contraction amplitude increases beat by beat until some plateau level is reached, the PSP phenomenon being absent (Koch-Weser and Blinks 1963; Khodorov et al. 1977). In order to find out how the Kaufmann's (1974) model should be modified to achieve an adequate description of the force-frequency phenomena of amphibian myocardium, we have examined the

dependence of RIR of the model upon the values of its parameters. To do this the model was first fed in to a digital computer. In the course of our computer experiments the numerical values of model coefficients were adjusted; this allowed to simulate RIR typical of most warm-blooded species (cf. legend to Fig. 2*A*).

The main results of these computer experiments with Kaufmann's model are presented in Fig. 2. The two-phase staircase characteristic of mammalian myocardium is shown in Fig. 2*A*, with relevant coefficient values and detailed specification of conditions of computer experiments given in legend to Fig. 2*A*. Figs 2*B* and 2*C* show that the initial two-phase staircase can be transformed into a monophasic ascending one either by diminishing k_0 (i.e. by decreasing the stationary Ca^{2+} influx) or by markedly elevating k_3 (i.e. by accelerating Ca^{2+} translocation from the central part of SR to the terminal cisternae). Note, however, that the decrease in k_0 per se, while preventing the formation of the two-phase staircase, fails to eliminate the transient increase in Ca^{2+} content in lateral cisternae of SR that occurs immediately after the cessation of stimulation (see Fig. 2*B*). Meanwhile, an increase in k_3 with k_0 fixed at its initial level removes both the PSP and the Bowditch staircase (Fig. 2*C*). Only a simultaneous decrease in k_0 and increase in k_3 (Fig. 2*D*) makes it possible to simulate the ascending staircase characteristic of frog myocardium. Under this condition the Ca^{2+} content in SR after the end of repetitive stimulation declines gradually to its initial level.

The above evidence suggests that for the simulation of RIR of amphibian myocardium one should assume that: i) no appreciable lag exists in Ca^{2+} translocation within the intracellular Ca stores, i.e. in amphibian myocardium these stores have a one-compartment structure (see scheme in Fig. 2*B*); ii) the contribution of the stationary component to the net Ca^{2+} influx during excitation is relatively small (compare the values of the relevant coefficients in legends to Fig. 2*A* and 2*D*).

Finally, the following simplified model of ECC in frog myocardium was obtained:

$$\begin{cases} \dfrac{dc}{dt} = k_0 + \alpha k_1 - k_2 c + \alpha k_4 rc - k_5 c + k_6 m \\ \dfrac{dr}{dt} = k_2 c - \alpha k_4 rc - \alpha k_7 r - k_8 r \\ \dfrac{dm}{dt} = k_5 c - k_6 m \end{cases} \tag{1}$$

Here, c is the Ca^{2+} content in the myoplasm, r is the Ca^{2+} content in the intracellular stores, m is the Ca^{2+} content in the mitochondria ("slow organelles"), all the above variables being expressed in relative dimensionless units; $\alpha(t)$ is a stepwise function describing the potential-dependent Ca^{2+} movements: α equals

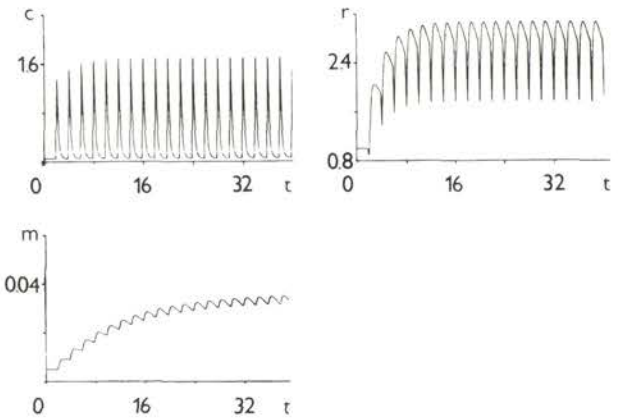

Fig. 3. The staircase phenomenon in model (1) of ECC in the frog myocardium. Periodic stimulation (frequency 0.5 Hz, AP duration 0.2 s) after a long rest is simulated. The content of Ca^{2+} in the myoplasm (c), in intracellular calcium pools (r) and in mitochondria (m) is shown. The coefficient values are given in Table 1.

unity during AP and zero during the rest of time; k_0 and k_1 are rate constants for the stationary and potential-dependent Ca^{2+} influxes, respectively; k_2 and k_4 are rate constants for the movement of Ca^{2+} into and out of the intracellular pool; k_5 and k_6 are constants for opposite Ca^{2+} currents in "slow" organelles; k_7 and k_8 are rate constants for potential-dependent and stationary currents outside the pool, respectively. All the rate constants are expressed in s^{-1}. Standard values of coefficients of the system (1) are summarized in Table 1.

The mathematical model suggested, as well as that of Kaufmann, lacks detailed mathematical description of particular mechanisms for Ca^{2+} ions transfer between the subcellular compartments. Instead, the influx of Ca^{2+} to the myocardial cell $(k_0 + \alpha k_1)$, the outflow from the cell $(\alpha k_7 r + k_8 r)$ change in a stepwise manner at the moments of membrane depolarization or repolarization due to the $\alpha(t)$ function which is incorporated into the relevant model equation terms as a multiplicative factor. For a more detailed discussion of the physiological background of the adopted model structure see Bassingthwaighte and Reuter (1972) and Kaufmann et al. (1974). This approach implies that e.g. the value of k_1 expresses the sum of individual contributions of slow inward current via Ca-channels and Ca^{2+} influx via Na-Ca exchange to the net influx of Ca^{2+} to myoplasm during AP; the active transport of Ca^{2+} to the intracellular stores corresponds to value k_2; the autoregenerative release of Ca^{2+} from the stores corresponds to coefficient k_4, etc. The Na-Ca exchange, which is known to be potential-dependent (Horackova and Vassort 1979) contributes to the constant k_1 and especially to constants k_7 and k_8 describing the removal of Ca^{2+} ions from the myocardial cell.

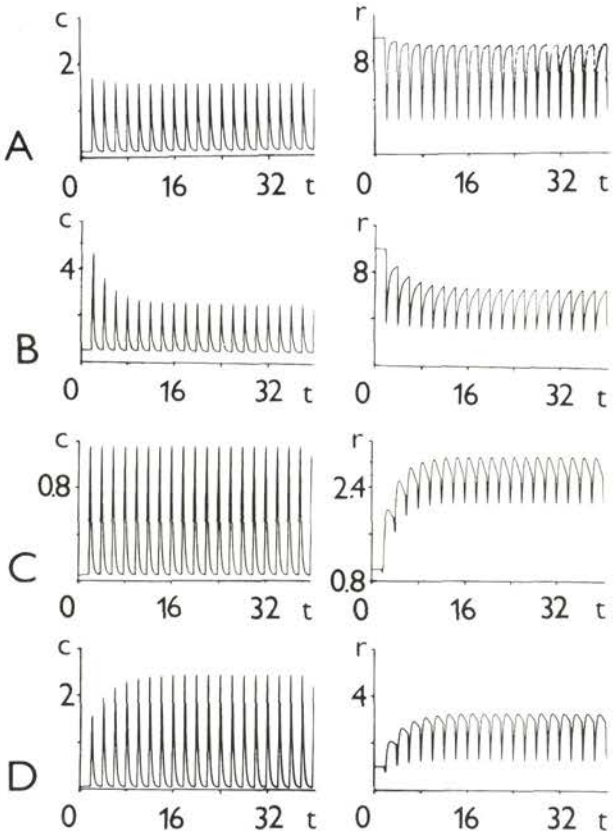

Fig. 4. The effect of calcium influx from the cell environment and intracellular stores on the shape of the staircase in model (1). Periodic stimulation (frequency 0.5 Hz, AP duration 0.2 s) after a long rest is simulated. The graphs on the left correspond to Ca^{2+} content in the myoplasm (c), the graphs on the right, to that of intracellular pools (r), the abscissa shows time in seconds. The coefficient values are: (s^{-1}): *A*) $k_0=2$; *B*) $k_0=2$, $k_1=1$; *C*) $k_4=0$; *D*) $k_4=4$. Other values in each panel are standard (see Table 1).

Table 1. Standard values of coefficients for model (1)

k_0, s^{-1}	k_1, s^{-1}	k_2, s^{-1}	k_4, s^{-1}	k_5, s^{-1}	k_6, s^{-1}	k_7, s^{-1}	k_8, s^{-1}	T, s	D s
0.2	8	4	2	0.01 (0)	0.1	2	0.2	2	0.2

T is stimulation period, D is duration of AP.

Table 2. The effect of some subcellular Ca^{2+} movements upon the staircase shape for model (1)[i].

Coefficient of the deviated model[ii]	Response to an increase in the coefficient
k_1	Increase in contractile force, increment in the staircase "steepness"
k_2	Lowering of the amplitude and shortening of the duration of relaxation phase in individual contractions; decrease in the staircase time constant (the time to reach the plateau level of contraction amplitude)
k_5, k_6	Changes in the staircase shape are insignificant
k_7, k_8	Lowering the contractile amplitude, significant decrease of the staircase time constant (especially in response to variation of k_8)

Notes: i) Conditions of simulation are shown in the legend to Fig. 4.
ii) Other values of coefficients in each case are standard (see Table 1).

The model (1) can reproduce the main force-frequency effects characteristic of the amphibian myocardium: changes of the steady state contraction amplitude with stimulation frequency; transient processes in response to multiple stepwise alterations of excitation frequency; the modification of the staircase time course due to various agents affecting rhythm-dependence of AP duration (Mukumov et al. 1978). An analysis of the results of computer experiments with the model (1) at above-listed excitation modes is presented below.

Analysis of the ECC model for frog myocardium

The simulations performed allowed us to obtain RIR of the model (1) at standard coefficient values and to compare these relationships with those at deviated model coefficients.

The Bowditch staircase obtained with standard values of the coefficients (Table 1; see also Pratusevitch et al. 1982) is presented in Fig. 3.

Fig. 4 shows an example of the staircase shape computed on deviating several model coefficients from their standard numerical values. Effects of variation of other coefficients are summarized in Table 2.

The conditions of the computation experiment were always the same; the "cell" being fed with squarewave depolarisation pulses at a frequency of 0.5 Hz and a duration of 0.2 s which imitate AP. The values recorded were the time course of Ca^{2+} content in the myoplasm and in the intracellular Ca-stores. The shape of the staircase was shown to be most easily modified by changes in the value of k_0 or in the ratio $k_0 : k_1$.

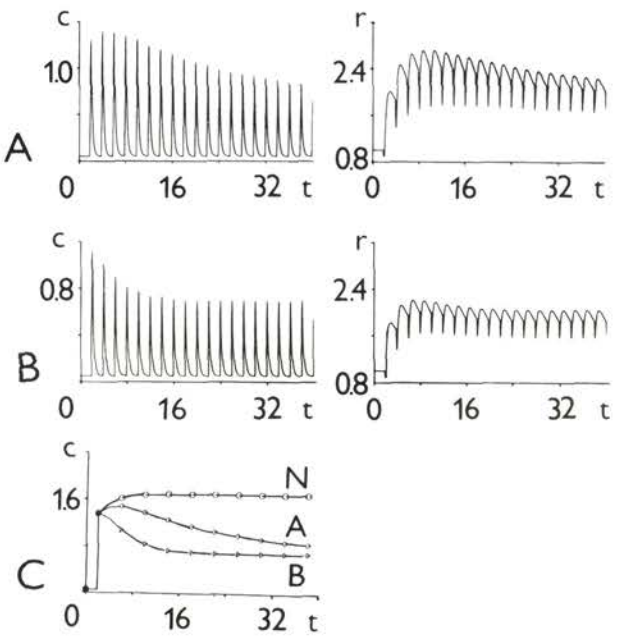

Fig. 5. Variation in the shape of the staircase in model (1) with decreasing AP duration in rhythmic stimulation, by the exponential law:

$$D = D_0(0.4 + 0.6 \exp(-t/\tau)$$

Periodic stimulation (frequency 0.5 Hz, the initial AP duration $D_0 = 0.2$ s) after a long rest is simulated. *A* and *B* show variation of Ca^{2+} content in the myoplasm (c) and in intracellular pools (r) for different rates of AP shortening: $\tau = 20$ s (A) and $\tau = 4$ s (B). *C* shows a comparison of staircase envelopes, $c(t)$. for normal conditions (curve N) and for exponential AP shortening with $\tau = 20$ s and $\tau = 4$ s (curves A and B, respectively).

Under normal conditions, the stationary Ca^{2+} influx (k_0) is low, and so is the initial Ca^{2+} stored in a resting cell (see Fig. 3). The pool is replenished during repetitive stimulation owing to the potential-dependent component of calcium current (k_1), which leads to an increase in contractile force. Calcium ions enter the myoplasm during each depolarization both from the extracellular medium (αk_1) and from the intracellular pool ($\alpha k_4 rc$). The amount of calcium released by the pool increases beat by beat owing to the rereplenishment of the pool, thereby resulting in increased amplitude until an equilibrium is reached.

As Fig. 4*A* ($k_0 = 2$) shows, an increase in k_0 may abolish the positive staircase

or even convert it into a negative one, while strengthening all the repetitive contractions due to a greater influx of Ca^{2+} from outside and a sharp increase in the level of pool filling. If this is accompanied by a decrease in the potential-dependent calcium influx ($k_1 = 1$ in Fig. 4*B*) a typical negative (steadily descending) staircase ensues. As Figs. 4*A* and 4*B* imply, decreasing k_1 after a period of rest causes a greater reduction of the steady-state force than of that of the first beat. This is due to the fact that the initial level of pool filling is determined only by the ratio of k_0 to k_8 and is independent of k_1.

The coefficient k_4 is related to the release of calcium from the intracellular pool, which is non-linear in character. If k_4 is reduced to zero (Fig. 4*C*) no staircase can arise: the myoplasm is uncoupled from the pool, and the first equation of system (1) contains no variable r. If k_4 is increased to 4 (Fig. 4*D*), the steady-state force and, to a lesser degree, the force of the first beat becomes greater owing to a greater portion of Ca^{2+} provided by the pool (cf. Fig. 3).

Fig. 5 shows the shape of the staircase (obtained with standard values of coefficients) as a function of AP duration, D. It can be seen that the Bowditch staircase can be converted into a negative (Woodworth) staircase with all the coefficients left unchanged. The model assumes here an exponential drop of AP duration from 0.2 to 0.08 s with different time constants (Fig. 5*A* and 5*B*). In the case of a smooth drop (Fig. 5*A*) the contractions become stronger at first, owing to the accumulatory properties of the pool. A subsequent drop, however, leads to a shortage of calcium entering the cell and hence a decrease in contraction force. When the drop of D is rapid (Fig. 5*B*) the result is a negative staircase lacking the initial ascending phase. Both of these responses may be observed in experiments with the frog myocardium under its exposure to pharmacological agents that shorten AP, e.g. Ca-channel blockers (Bayer et al. 1975). For demonstration purposes, Fig. 5*C* shows envelopes of staircases for $D = \text{const}$, $D = 0.2(0.4 + 0.6e^{-0.05t})$ and $D = 0.2(0.4 + 0.6e^{-0.25t})$ (the coefficients have standard values in each case).

The model is able to qualitatively reproduce the characteristics of frog myocardium observed in experiments with complex modes of stimulation (Fig. 6; cf Mukumov et al. 1978). We subjected our model to the following change of stimulation frequencies: 0.2 Hz – 0.5 Hz – 1 Hz – 0.5 Hz – 0.2 Hz. For the standard values of coefficients (see Fig. 6) the transition to a higher frequency was always accompanied by a transient process associated with increased amount of Ca^{2+} released by the pool (a rise in frequency leads to a progressive rise in the maximum content of Ca^{2+} in the pool). A return to initial frequencies completely restored the original pattern.

In the model of Kaufmann et al. (1974) Ca^{2+} can be removed from the myoplasm only via SR. Such an assumption is justified by certain morphological evidence in the case of myocardium of warm-blooded animals but is contentious

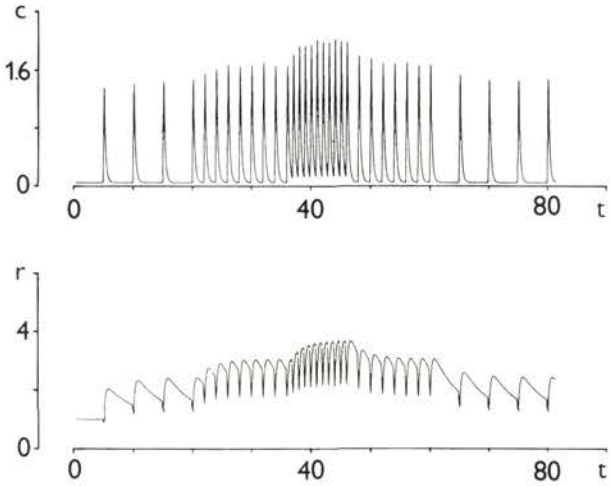

Fig. 6. Rhythmic stimulation in model (1) at varied frequency: 0.2—0.5—1.0—0.5—0.2 Hz. Ca^{2+} content in the myoplasm (c) and intracellular pools (r) at the standard set of coefficients (Table 1) is shown as a function of time (t, s).

with regard to frog myocardium where the T-system and the SR are represented very poorly (Page and Niedergerke 1972). We attempted to use our model for testing the assumption that, in the frog, Ca^{2+} is transported to the cellular environment mainly from the myoplasm. For this purpose an additional term, $-k_9 c$, corresponding to a direct transport of calcium from the myoplasm outside was added to the equation system (1). The studies have shown, however, that the modified model fails to simulate some experimental observations. We interpret this fact as suggesting that Ca^{2+} ions in the amphibian myocardium are transported from the myoplasm to the extracellular media not directly but mainly via intracellular pools. It may by hypothesized that the morphological entity corresponding to Ca^{2+} pools in the frog myocardium not only is the poorly developed SR but also the inner side of the sarcolemma. Support for this hypothesis seems to be offered by some experimental data (Izakov 1974; Khodorov et al. 1977; Mukumov et al. 1984).

Conclusions

The present analysis indicates that the simplified mathematical model (1) of ECC can reproduce most of the basic rhythm-inotropic relations characteristic of the frog myocardium, with a fixed set of model parameters. This result provides some evidence in favour of the hypothesis of the essential role of intracellular Ca^{2+}-stores in controlling myoplasmic Ca^{2+} concentrations in frog heart muscle.

The mathematical model described is useful in attempting to elucidate the role of individual Ca^{2+} fluxes in the cell Ca-recirculation system and their effects on force frequency relationships in the frog myocardium (within the framework of the adopted working hypothesis).

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