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Original article

Function of the sodium-calcium exchanger during myocardial contraction-relaxation caused by strophanthin administration

Tatjana A. Berezhnova, Ivan P. Moshurov, Vladimir V. Alabovsky, Irina V. Kovalenko, Chaoqian Xu, Lei Yang

Tatjana A. Berezhnova, DSc (Medicine), Professor, Head of the Pharmacology Department, Voronezh State Medical University named after N.N. Burdenko, 10, Studencheskaya str., Voronezh, 394036, Russia

Ivan P. Moshurov, DSc (Medicine), Professor, Acting Rector, Voronezh State Medical University named after N.N. Burdenko, 10, Studencheskaya str., Voronezh, 394036, Russia

Vladimir V. Alabovsky, DSc (Medicine), Professor of the Clinical Laboratory Diagnostic Department, Voronezh State Medical University named after N.N. Burdenko, 10, Studencheskaya str., Voronezh, 394036, Russia

Irina V. Kovalenko, Assistant of the Pharmacology Department, Voronezh State Medical University named after N.N. Burdenko, 10, Studencheskaya str., Voronezh, 394036, Russia

Chaoqian Xu, Professor, Department of Pharmacology, State-Province Key Laboratories of Biomedicine Pharmaceutics of China, Key Laboratory of Cardiovascular Medicine Research; College of Pharmacy, Harbin Medical University, Harbin, 150081, China

Lei Yang, Professor, Department of Orthopedics, The First Affiliated Hospital of Harbin Medical University, Harbin, 150001, China; State Key Laboratory of Frigid Zone Cardiovascular Diseases (SKLFZCD), Harbin Medical University, Harbin, 150081, China

ABSTRACT

Cardiac glycosides influence myocardial contractility via affecting Na^+–Ca^{2+} exchange, but the isolated contribution of this mechanism remains poorly understood.

Aim. To determine the effects of strophanthin on cardiac contractions generated by the sodium-calcium exchange system alone.

Materials and methods. Experiments were performed on isolated hearts of Wistar laboratory rats perfused through the aorta using the Langendorff technique. Contractions were induced by perfusion with solutions of varying Na^+ concentrations. Strophanthin in ampoules that was used as the studied pharmaceuticals was added to the perfusion medium at a final concentration up to 0.5 μmol/L. An equivalent volume of saline was administered in the control series.

ORCID numbers: Tatjana A. Berezhnova 0000-0002-8401-3460; Ivan P. Moshurov 0000-0003-1333-5638; Vladimir V. Alabovsky 0000-0002-6306-5149; Irina V. Kovalenko 0000-0002-3094-4307; Chaoqian Xu 0009-0001-9528-7985; Lei Yang 0009-0002-0830-0000

Correspondence to: Irina V. Kovalenko
E-mail: kovalenkoirin@gmail.com

Contributors: Tatjana A. Berezhnova: study concept and design, manuscript editing. Ivan P. Moshurov: study concept and design, manuscript editing. Vladimir V. Alabovsky: study concept and design. Irina V. Kovalenko: data analysis and interpretation, manuscript writing. Chaoqian Xu: manuscript editing. Lei Yang: data collection and interpretation.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.
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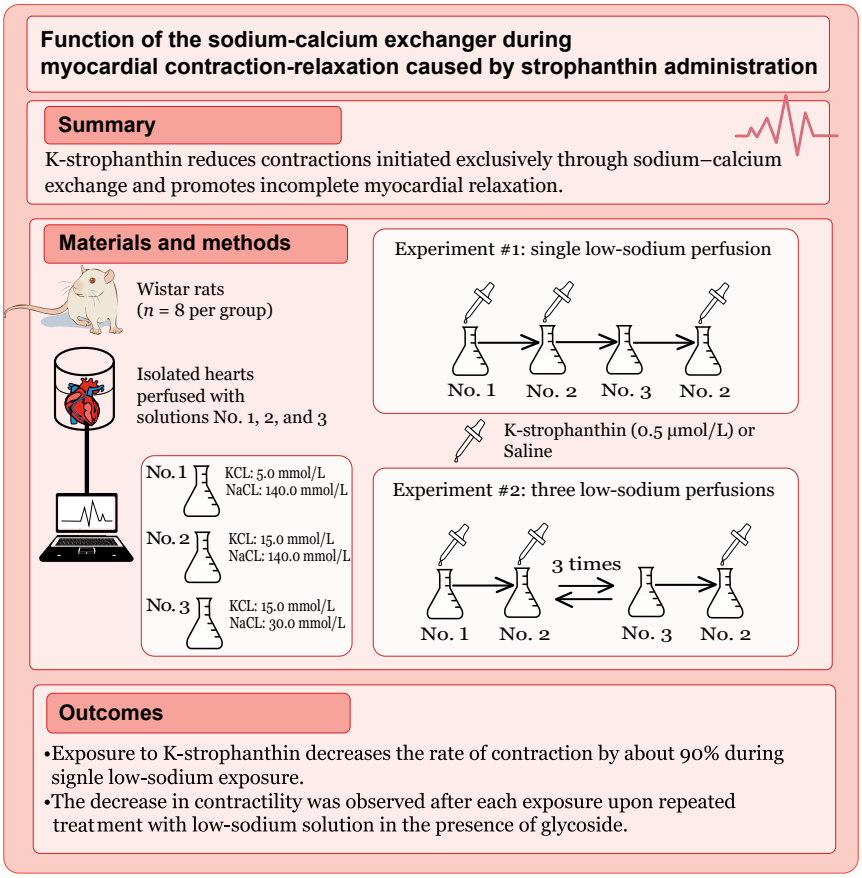
Results. Experiments showed that the heart continued to contract and relax with each cycle of Na^+–Ca^{2+}exchange activation. However, the rate of contraction in the second repetition was 32% lower. Strophanthin reduced contraction force in all three repetitions. Particularly significant disturbances were observed during the first stimulation — by 78%. Muscle contractions and relaxation occurred under gradual increase in muscle tone during diastole. Given that strophanthin can reduce the activity of the Na^+/K^+-Adenosine Triphosphatase (Na^+/K^+-ATPase), our experiments clearly demonstrated the glycoside's ability to increase intracellular sodium, and consequently, calcium concentrations. Repeated calcium efflux from cells via Na^+–Ca^{2+}exchange proved ineffective in the presence of strophanthin. The heart continued to experience calcium overload, which was reflected in the increased cardiac diastole stress.

Conclusion. When cardiac cells experience calcium ion overload, the final physiological effect influenced by strophanthin may be negative rather than positive.

Graphical abstract



Key Words: Na^+–Ca^{2+} metabolism; strophanthin; cardiac calcium overload; sarcoplasmic reticulum; voltage-dependent channels; cardiac glycosides

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MeSH terms:

MYOCARDIAL CONTRACTION — DRUG EFFECTS;

MYOCARDIUM — METABOLISM;

STROPHANTHIDIN — PHARMACOLOGY;

SODIUM-CALCIUM EXCHANGER — DRUG EFFECTS

Introduction

In clinical practice, pharmaceuticals that enhance the functional capacity of the cardiac muscle are widely used. Cardiac glycosides, such as strophanthin, which has a pronounced positive inotropic effect, are of special significance among them. The pharmacological effect of glycosides is associated with their ability to inhibit Na^+/K^+-Adenosine Triphosphatase (Na^+/K^+-ATPase) in the cell membrane. Blockade of this enzyme leads to an increased intracellular sodium content, which activates Na^+–Ca^{2+} exchange carried out by a specialized transporter in the outer membrane of cardiomyocytes [2, 3]. The Na^+–Ca^{2+}transporter protein is capable of binding and transporting ions of both types; however, at rest, the Na^+ and Ca^{2+} interaction with its active site is balanced, and practically no transport is performed. When the sodium concentration in the cytoplasm increases under the influence of glycosides, Na^+ obtains an advantage, and the exchanger starts to effectively remove sodium from the cell replacing in exchange for calcium. This results in an increase in the intracellular mobile fraction of Ca^{2+} circulating between the cytosol and the sarcoplasmic reticulum, and consequently an enhanced myofibrils activation and increased contraction force. Under normal conditions, cardiomyocyte contraction is triggered by a small amount of calcium entering through L-type calcium channels during electrical stimulation. This initial influx serves as a stimulus for ryanodine receptors, causing a massive release of Ca^{2+} from the reticulum [4].

This mechanism has been well studied, but the involvement of Na^+–Ca^{2+} exchange as a secondary mechanism for activating calcium release remains controversial. As supposed, an increased local sodium concentration in the subsarcolemmal space under fast sodium channels opening during an action potential can enhance Ca^{2+} entry via Na^+–Ca^{2+}exchange [5, 6]. During depolarization by fast Na^+ currents, sodium concentration at the inner surface of the membrane increases, and excess sodium is exchanged for extracellular calcium. As a result, intracellular Ca^{2+} increases which may further contribute to the activation of ryanodine receptors [7].

Since the activity of Na^+–Ca^{2+} exchange is determined by the level of intracellular Na^+, and cardiac glycosides significantly increase its content, the action of the second triggering mechanism can be significantly altered [3]. A decrease in the sodium gradient weakens the Na^+ in flux during the action potential and can reduce the efficiency of Ca^{2+} entry mediated by Na^+–Ca^{2+} exchange. Therefore, the extent to which cardiac glycosides are able to modify the force of cardiac contractions arising exclusively through Na^+–Ca^{2+} exchange remains unknown. To clarify this, it is necessary to exclude all other pathways for Ca^{2+} and Na^+ ion influx through channels and to initiate contraction through Na^+–Ca^{2+} exchange alone.

An important prerequisite for studying the sodium-dependent movement of calcium ions across the muscle sarcolemma is the elimination of other calcium fluxes. Calcium ions can enter cells through slow calcium channels and be excreted by Ca^{2+} pumps. Fast sodium channels may also be involved in the regulation of intracellular Ca^{2+} levels. The appearance of sodium ions inside cells can also alter the Na^+–Ca^{2+} exchange process, this additionally being an interfering factor when assessing the function of the sodium-calcium exchanger alone [7]. Therefore, the best way to eliminate these interferences, in the study of exclusively Na^+–Ca^{2+} exchange, is the complete shut-off of sodium and calcium channels by depolarisation of cardiomyocyte membranes.

The aim of this study was to determine the nature of strophanthin effect on the calciumdependent mechanical activity of the heart triggered exclusively through the sodium-calcium exchange mechanism.

Materials and methods

Laboratory animals

Thirty-two mature male Wistar rats weighing between 180 and 250 g, and aged 2–3 months were used in a series of experiments. Animals were obtained from the Research Institute of Experimental Biology and Medicine of the N.N. Burdenko Voronezh State Medical University. The experiments were conducted in accordance with the recommendations of the Eurasian Economic Commission No. 33. The studies were approved by the local independent ethics committee, N.N. Burdenko Voronezh State Medical University (Protocol No. 5 dated 19.09.2023).

Isolation of heart

Animals were euthanized by decapitation using a desiccator under general anesthesia with diethyl ether. Immediately after thoracotomy, the isolated heart was placed in cooled (2–4 °C) Krebs—Henseleit solution. After spontaneous contractions ceased, the heart was cannulated through the aorta, and cardiac perfusion was performed. Perfusion was performed at a stable rate of 9 ml/min per 1 g of wet heart weight. There were two experiments performed. Each experiment involved 16 animals: 8 rats in control group and 8 animals in experimental group.

Equipment and perfusion solutions

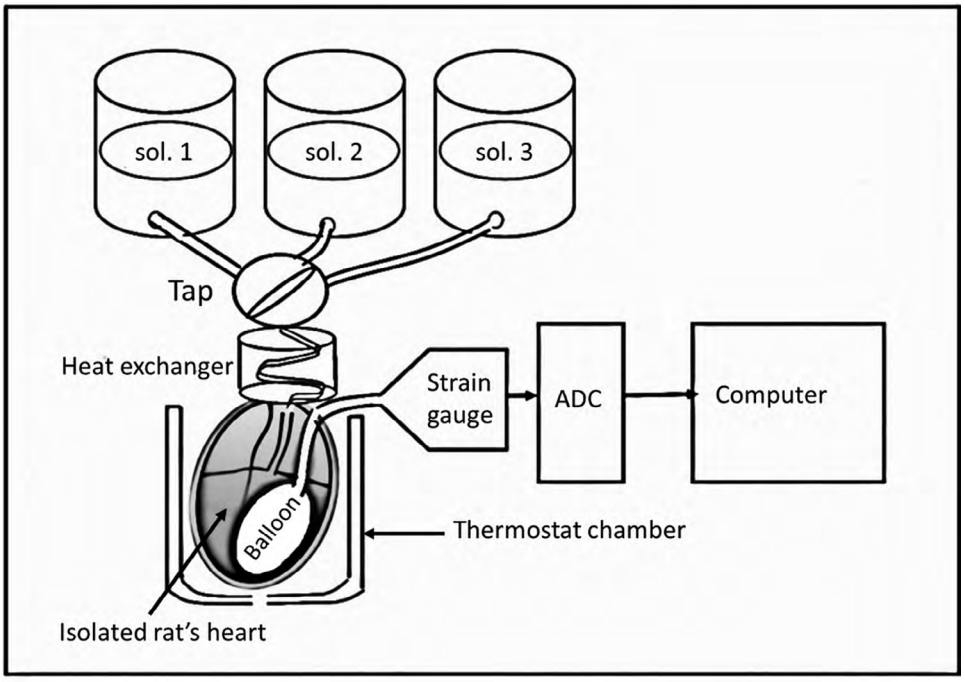
Elastic balloons were fixed in the left ventricular cavity and connected to an electronic pressure sensor. The described construction was used to record contractile parameters. Sensor signals were amplified, sent to an analog-to-digital converter, and then analyzed using the Zet Lab software module connected to a personal computer (Figure 1). Zet Lab software was used to record and process the studied parameters. Such a model has already been successfully employed by us in the course of other studies [8].

Oxygenated Ringer-Locke solution (solution No. 1) was used as the base perfusion solution at 37 °C. Solutions No. 2 and No. 3 characterized by an increased potassium chloride concentration of 15 mmol/L and used to create depolarization conditions. The increased K^+ level led to persistent depolarization of the cardiomyocyte membrane; thus, sodium and calcium voltage-gated channels lost their ability to open in response electrical activity.

The composition of the perfusion solutions used is presented in Table 1.

After the isolated heart was connected to the perfusion apparatus, stabilization of cardiac function was achieved by perfusing with solution No. 1 for 10 minutes. The heart was switched to solution No. 2 containing a three-fold concentration of KCl before the activation of sodium-calcium exchange. This technique resulted in a complete cessation of electrical and mechanical activity, eliminating the entry of Ca^{2+} through L-channels and the Na^+ current associated with action potential [9]. Thus, the only mechanism remained capable of initiating the release of Ca^{2+} from the sarcoplasmic reticulum and causing contraction was Na^+–Ca^{2+} exchange. Sodium-dependent calcium influx was initiated by replacing the standard solution with hyponatremic solution No. 3, in which the NaCl concentration was reduced from 140 to 30 mmol/L. With reduced sodium concentration in the extracellular medium,

FIG. 1. Schematic diagram of a device recording cardiac contractions via Na^+–Ca^{2+} exchange [8]



Note: ADC — analog-to-digital converter; sol. — solution.

Table 1. Composition of perfusion solutions

Components	Solution No. 1	Solution No. 2	Solution No. 3
NaCl	140.0	140.0	30.0
$NaHCO_3$	2.0	2.0	2.0
KCl	5.0	15.0	15.0
Tris-OH (pH = 7.4)	2.0	2.0	2.0
$CaCl_2$	2.0	2.0	2.0
Glucose	11.0	11.0	11.0
Mannitol	–	–	220.0

Note: all concentrations are given in mmol/L.

calcium ions obtained an advantage while interacting with the Na^+–Ca^{2+}-exchanger on the outer membrane surface, leading to increased Ca^{2+} entry into cells. The decrease in osmolarity of the hyponatremic solution No. 3 was compensated by adding mannitol (up to the final concentration of 220 mmol/L). After 5-min perfusion with the hyponatremic solution No. 3, it was replaced with the solution No. 2, containing NaCl and KCl at their original concentrations of 140 mmol/L and 15 mmol/L, respectively. Under these conditions, the direction of Na^+–Ca^{2+} exchange was reversed: excess extracellular Na^+ entered the cells, while Ca^{2+} was removed from the cytosol.

The sequence of solutions' application in first experiment was as follows: solution No. 1 (10 min) → solution No. 2 (5 min) → solution No. 3 (5 min) → solution No. 2 (5 min).

Following the first experiment (16 rats), a second experiment was performed. It involved three consecutive activations of the Na^+–Ca^{2+} exchanger to elucidate the mechanisms underlying the effect of K-Strophanthin (hereafter referred to as strophanthin) on calcium regulation of myocardial contractility. The sequence of solutions' application in the second experiment was as follows: solution No. 1 (10 min) → [solution No. 2 (5 min) → solution No. 3 (5 min)] × 3 times → solution No. 2 (5 min).

Strophanthin in ampoules was added to the perfusion medium of the solutions No. 1 and No. 2 that were used in experimental groups to a final concentration up to 0.5 μmol/L. An equivalent volume of saline was administered to the solution used in animals of the control group.

The complete experimental design is presented in Figure 2.

FIG. 2. The experimental design for studying the effect of strophanthin on the function of the Na^+–Ca^{2+} exchanger

First experiment:

Control: Saline (8 rats)

Experimental: 0.5 μmol/L strophanthin (8 rats)

Sol. 1	Sol. 2	Sol. 3	Sol. 2
10 min	5 min	5 min	5 min

Second experiment:

Control: Saline (8 rats)

Experimental: 0.5 μmol/L strophanthin (8 rats)

Sol. 1	Sol. 2	Sol. 3	Sol. 2	Sol. 3	Sol. 2	Sol. 3	Sol. 2
10 min	5 min	5 min	5 min	5 min	5 min	5 min	5 min

Note: Sol. – solution.

Statistical analysis

Statistical data were processed using repeated-measures analysis of variance (RM-ANOVA). The normality of distribution was assessed using the Shapiro–Wilk test. The significance of differences between the mean values of the experimental and control groups was assessed using paired *t*-test (when comparing between time points) and independent Student's *t*-test (when comparing between groups). Differences were considered statistically significant in $p < 0.05$. Statistical data were analyzed using StatSoft (TIBCO Statistica 14.1.0).

Results

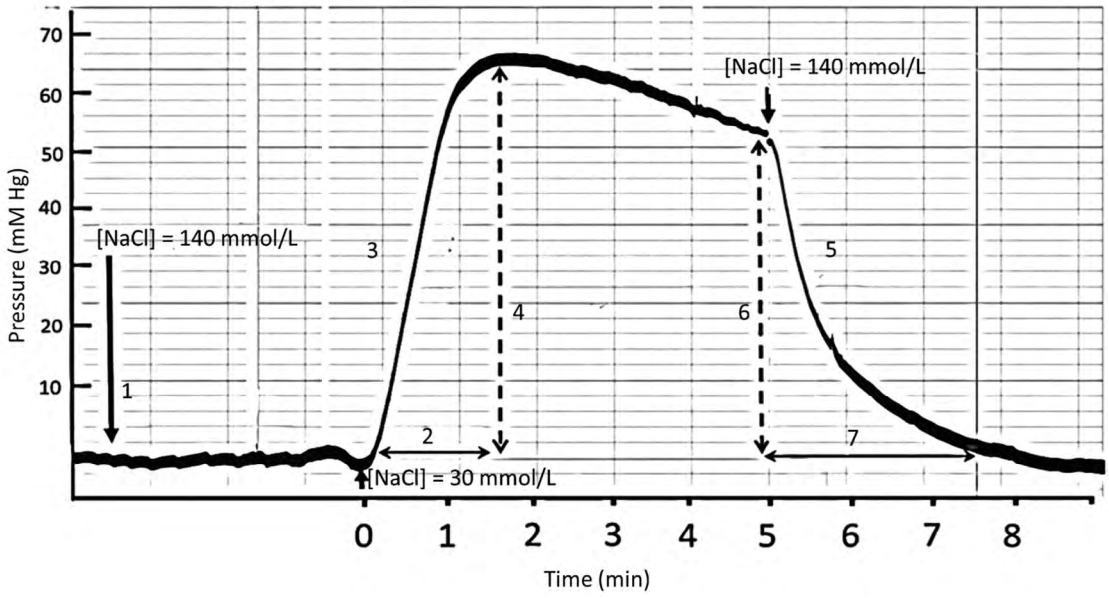
All experiments were conducted under complete asystole. This approach fully eliminated the involvement of calcium currents through L-type channels, as well as the inward sodium currents that accompanied action potential. This allowed the occurrence of mechanical activity to be associated exclusively with the functioning of the Na^+–Ca^{2+} exchange mechanism.

Cardiac response to strophanthin during a single low-sodium perfusion

The Na^+–Ca^{2+} exchanger activation by decreased extracellular sodium levels under the control conditions resulted in left ventricular contraction (Figure 3). The contraction demonstrated its maximum pressure, reaching 63 mmHg, approximately 74 seconds after the onset of hyponatremic solution perfusion.

Reversion to a solution with a normal NaCl concentration within five minutes caused gradual muscle relaxation and restoration of the initial tone. These observations confirmed that altering the direction and intensity of the Na^+–Ca^{2+} exchanger allowed both initiating and terminating the left ventricular mechanical activity. Thus, Na^+–Ca^{2+} exchange under these conditions influenced not only the force of contraction but also the relaxation phase of the myocardium.

FIG. 3. Recording changes in pressure in the left ventricle of the heart under the activation of Na^+–Ca^{2+} exchange via changing the extracellular concentration of sodium chloride

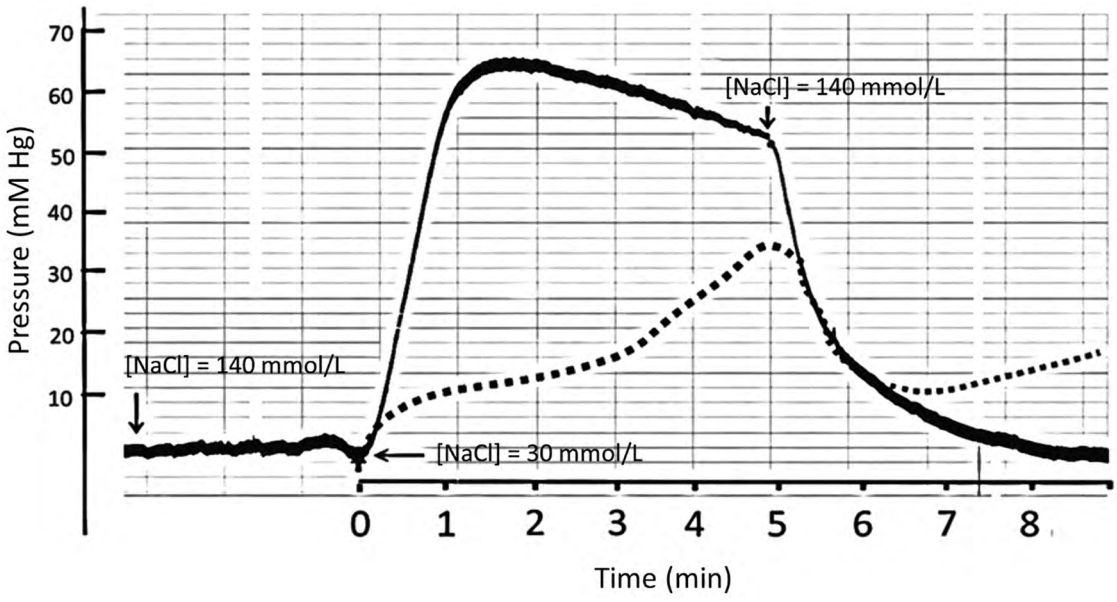


Note: 1 – initial pressure, 2 – T1 contraction, 3 – V Contraction, 4 – H1 max contraction, 5 – V Relaxation, 6 – H2 min relaxation, 7 – T2 relaxation.

The tension parameters, the rate of contraction increase, and the rate of relaxation were subjected to mathematical analysis, which allowed developing a model for further evaluation of the strophanthin effect under conditions where contractility was regulated exclusively by the Na^+–Ca^{2+} exchange system.

After pre-perfusion with a solution containing strophanthin, Na^+–Ca^{2+} exchange was activated by reducing the extracellular Na^+ concentration to 30 mmol/L. The cardiac response in this case was significantly different from the control (Figure 4).

FIG. 4. The strophanthin effect on the dynamics of contraction and relaxation of the rat heart caused by the Na^+–Ca^{2+} exchange activation



Note: the dashed line indicates the values of the experimental group (n = 8) that received strophanthin, and the solid line indicates the values of the control group (n = 8) that was administered saline.

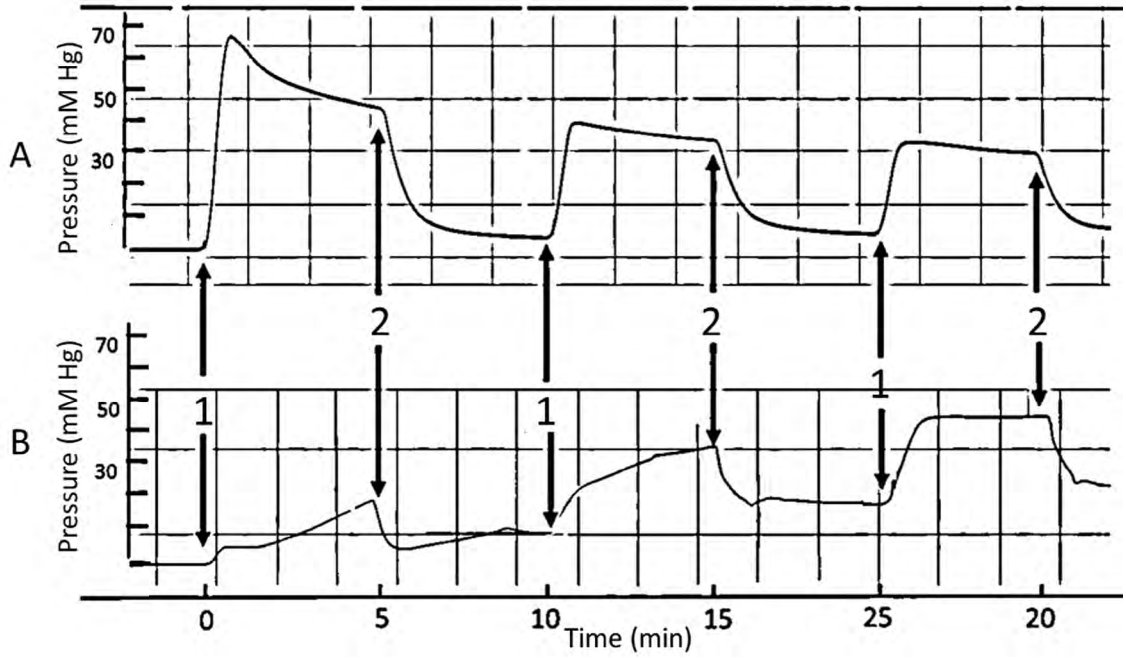
There was a sharp decrease in the rate of contraction development—approximately 90%. Maximum contractile force decreased by 80%. Even after 5-min-perfusion via a hyponatremic solution, tension levels remained 50% lower than the control values. These data indicated a significant strophanthin effect on myocardial contractility via calcium regulation.

Cardiac response to strophanthin during three successive low-sodium perfusions

The next step was to determine how strophanthin influences cardiac contractility under repeated stimulation of Na^+–Ca^{2+} exchange. Accordingly, we performed additional experiments, including three successive exchanger activations via extracellular Na^+ reduction.

The heart retained its ability to contract and relax with each cycle of Na^+–Ca^{2+} stimulation. However, in the second cycle, the rate of contraction development decreased by 32% compared to the first cycle (Figure 5).

FIG. 5. Strophanthin effect on repeated contractions and relaxations of the heart stimulated by Na^+–Ca^{2+} exchange



Note: the recordings of changes in left ventricular pressure during repeated activations of Na^+–Ca^{2+} exchange in the control group (A) and the experimental group (B). The activation was performed with varying concentrations of NaCl — 30 mmol/L (1) and 140 mmol/L (2). The number of animals was 8 in each group.

Strophanthin reduced contractile force in all three repeated activations, most significantly in the first (by 78%), then in the second (by 24%), and to the least extent in the third (by 20%). A gradual increase in diastolic tone was observed (Table 2), indicating incomplete muscle relaxation after each cycle.

The fact that the heart maintained its ability to respond to repeated changes in the direction of Na^+–Ca^{2+} exchange indicates that the exchanger continued to function even in the presence of strophanthin. Furthermore, the preservation of contractile responses during repeated activations confirmed the sarcoplasmic reticulum functionality. Thus, repeated cycles of Na^+–Ca^{2+} exchange activation in the presence of strophanthin were accompanied by an ever-growing decrease in the amplitude of incoming calcium flows and resulted in weakened contractions.

Table 2. Strophanthin effect on the values of Na^+–Ca^{2+} exchange reactions during three successive contractions and relaxations

Parameters	The number of repeated Na^+–Ca^{2+}exchanges			
	Experiments	1st cycle	2nd cycle	3rd cycle
V1, the rate of increased systolic tone ($dP/dt_{max}/c$)	control	1.31 ± 0.02	1.25 ±0.03	1.20 ± 0.04
	strophanthin	0.13 ±0.01**	0.85 ± 0.06** #	1.10 ± 0.05#
V2, the relaxation rate ($dP/dt_{max}/c$)	control	0.98 ± 0.03	0.94 ± 0.02	0.91 ± 0.03
	strophanthin	0.87 ± 0.04*	1.05 ± 0.04* #	0.84 ± 0.05
Maximum contractile force, H1 (mmHg)	control	63 ± 1.3	58 ± 1.4#	55 ± 1.1#
	strophanthin	14 ± 1.0**	44 ± 1.9** #	44 ± 1.7* #
Contractile force in 5 minutes of 30-mM-NaCl perfusion, H2 (mmHg)	control	49 ±1.4	48 ±1.06	48 ± 1.0
	strophanthin	26 ± 1.3**	38 ± 1.9** #	36 ± 1.4*#
The time period from the onset of the Na–Ca exchange initiation to the maximum reduction, T1 (sec)	control	74 ± 2.1	77 ± 1.2	72 ± 1.5
	strophanthin	290 ± 14**	81 ± 2.1#	78 ± 0.9#
The time period from the onset to complete muscle relaxation, T2 (sec)	control	130 ± 2.7	125 ±3.2	117 ± 2.4
	strophanthin	125 ± 6.4	118 ± 5.7	116 ± 2.9

Note: data is presented as the mean ± standard error of the mean (SEM); * — $p < 0.05$ and ** — $p < 0.01$ by independent Student's *t*-test when compared with control; # — $p < 0.05$ by paired *t*-test when compared with 1 record within the same group. Both control and experimental groups included 8 rats.

Calcium removal upon returning to normal sodium solution was also incomplete: although the rate and duration of the relaxation phase did not differ from the control, the initial tone level remained elevated in each case. Thus, strophanthin maintained a chronically elevated Ca^{2+} concentration in cytosol throughout the experiment, leading to a persistent increase in diastolic tension and incomplete recovery of the muscle potentials between activation cycles.

Discussion

First, we should emphasize the validity of the chosen experimental technique. Conditions of complete electrical activity blockade and cardiac contractions cessation allowed recording mechanical responses arising exclusively via the sodium-calcium exchange mechanism.

A distinctive feature of the identified process was that contractions developed significantly more slowly than under physiological conditions of electromechanical activation. This indicated that calcium entering cells via Na^+–Ca^{2+} exchange not only triggered the release of ions from the sarcoplasmic reticulum but also directly activated the contractile apparatus. This assumption is consistent with Lehnart et al. who demonstrated the ability of calcium entering via Na^+–Ca^{2+} exchange to interact with the contractile structures of cardiomyocytes [10].

Furthermore, Na^+–Ca^{2+} exchange, under certain conditions, has the potential to provide a sufficient Ca^{2+} influx to maintain contractile activity even during a normal action potential. For example, it has been shown that blockade of the Na^+–Ca^{2+} exchanger led to a shortening of the action potential and a marked reduction in contractile force [11].

It is important to note that the maximum pressure developed in the rat left ventricle with sodium-dependent Ca^{2+} influx was comparable to the level observed in physiological and pathological conditions of the heart [12]. These data confirm the validity of the chosen approach to analyze the effect of glycosides on the calcium exchange mechanism regulating contractility.

Strophanthin reliably increases intracellular calcium levels via Na^+/K^+-ATPase inhibition and activation of the Na^+–Ca^{2+} exchange. This compound was chosen as a model medication to evaluate the effect of glycosides on

the activity of Na^+-Ca^{2+} exchanger. In clinical practice, however, strophanthin requires caution: in severe heart failure, arrhythmia, or ischemic injury, the use of glycosides is limited due to the potential for deterioration in energy metabolism and electrolyte balance [13, 14].

The positive inotropic effect of strophanthin is associated with an increase in the free fraction of intracellular calcium. However, in various pathological conditions, decreased activity of the Na^+–K^+ pump itself can lead to accumulation of intracellular Na^+ and a secondary increase in Ca^{2+} via Na^+–Ca^{2+}exchange. These processes accompany the development of local contractures and other disorders associated with myocardial contractility [10, 15].

Glycoside administration under pre-existing calcium overload can reduce rather than enhance cardiac performance and increase the risk of arrhythmia, as has been repeatedly reported in clinical observations [14, 16].

The study results confirm these concerns. As demonstrated, the developing myocardial calcium overload is the main factor in the pronounced weakening of contractions upon strophanthin treatment. These data are consistent with the idea that excess cytosolic Ca^{2+} can suppress the activity of the Na^+–Ca^{2+} exchanger at the stage of its direct action [17]. This is evidenced by the following experimentally observed phenomena:

- slowdown in the rate of contraction development;
- decrease in the maximum force of contraction;
- incomplete muscle relaxation under reversion to a normal sodium environment;
- gradual increase in diastolic tension.

These effects are particularly significant under conditions when strophanthin maintains elevated intracellular Na^+ levels for a long time. Sodium accumulation naturally leads to an increased Ca^{2+} concentration; the exchanger is unable to completely remove this excess under reversion to a normal sodium solution. This results in a persistently increased cardiac tone and incomplete relaxation after each cycle of Na^+–Ca^{2+} exchange activation.

The presented study has a number of limitations that should be acknowledged. The results came from experiments on isolated rat hearts that were prepared under conditions of artificial perfusion, thus, may not directly reflect all aspects of heart function *in vivo*. Also, the observed alterations of the perfusion rate may be impacted by the changes in heart muscle activity or individual parameters of each rat. The conclusions regarding changes in Na^+–Ca^{2+} exchange are based on indirect measurements. In particular, we did not measure Na^+/K^+-ATPase activity or the expression of transporter proteins. However, the correlation between heart contractility and the ionic composition of the environment is well known [18]. Therefore, in our opinion, these conclusions are reasonable and the importance of the results remains.

Conclusion

In this study, strophanthin reduced contractions initiated exclusively through Na^+–Ca^{2+} exchange and promoted incomplete myocardial relaxation. The data obtained demonstrate that the use of cardiac glycosides is only justified when the cellular ability to regulate intracellular Ca^{2+} levels is preserved. Under calcium overload, the cardiac glycoside effect may be unfavorable and, instead of enhancing, may actually suppress myocardial contractility.

These results additionally evidence that the efficacy and safety of glycosides are closely related to the initial state of ionic homeostasis of the cardiac muscle and should be taken into consideration during clinical use.

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