ORIGINAL ARTICLE

ISSN: 0331 - 670X

https://doi.org/10.51412/psnnjp.2025.035

The Nigerian Journal of PHARMACY
AS MEN OF HONOUR WE JOIN HANDS
THE OFFICIAL ORGAN OF THE PHARMACEUTICAL SOCIETY OF NIGERIA FOUNDED 1927

Cardiotonic Effects of Oral Antimalarial Drugs on *In-Situ* Frog Heart

Joseph Ayo Badejo, Oluwapelumi Andrew Eseola, Obaro Stanley Michael, Ezekiel Olugbenga Iwalewa.

Department of Pharmacology and Therapeutics, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Oyo State, Nigeria

ARTICLE INFO

Article history:

Received 30th May 2025
Revised 3rd August 2025
Accepted 5th September 2025
Online Published

Keywords:

Chloroquine;
artemether-lumefantrine;
artesunate;
frog heart;
cardiotoxicity;
chronotropic effect;
inotropic effect.

**Corresponding Author:*
Dr. O. S. Michael
Email: micobaro@gmail.com
Tel: +2348056642410

ABSTRACT

Background: Antimalarial drugs remain essential for malaria control, but concerns persist about their potential cardiovascular effects. Chloroquine, artemether-lumefantrine, and artesunate are widely prescribed, yet their impact on myocardial activity is incompletely understood. This study evaluated the cardiotonic effects of these drugs using an in-situ frog heart model.

Methods: Three frogs were pithed, and isolated heart preparations were mounted on a force transducer. Baseline heart rate, contraction amplitude (mV), and force of contraction (gram force, gF) were recorded. Chloroquine was administered at 10 mg/kg (therapeutic) and 100 mg/kg (supratherapeutic), artemether-lumefantrine at 4 mg/kg and 40 mg/kg, and artesunate at 4 mg/kg and 40 mg/kg. Saline served as control. Percentage changes in cardiac parameters relative to baseline were analyzed.

Results: Chloroquine produced a dose-dependent bradycardia, reducing heart rate from 75 bpm at baseline to 66 bpm at therapeutic and 60 bpm at supratherapeutic doses. Contractile amplitude fell modestly at the therapeutic dose (−3.7%) but increased at supratherapeutic concentration (+0.5%). Force of contraction decreased slightly at therapeutic dose (2.6 gF) but rose at higher concentration (2.8 gF) at supratherapeutic dose. Artemether-lumefantrine exhibited minimal cardiac impact: heart rate remained unchanged at therapeutic dose (39 bpm) and decreased only slightly at supratherapeutic dose (36 bpm). Contractile force fell consistently by 2.3% across both doses. Artesunate demonstrated a contrasting profile, increasing heart rate markedly at therapeutic dose (from 36 to 51 bpm) but reducing contractile amplitude (−18%) and force of contraction (from 11.7 to 9.6 gF). At supratherapeutic levels, heart rate rose to 42 bpm, while contractile force remained depressed (9.8 gF).

Conclusion: Chloroquine exerted a dose-dependent negative chronotropic effect, with paradoxical increases in contractility at higher doses, consistent with its cardiotoxic profile. Artemether-lumefantrine showed negligible cardiodepressive effects, reinforcing its safety. Artesunate induced pronounced tachycardia but reduced myocardial contractility, warranting further mechanistic studies. The in-situ frog heart model effectively revealed these drug-specific cardiac effects, highlighting the need for pharmacovigilance in antimalarial therapy.

INTRODUCTION

Malaria remains a major global health concern. Despite being both preventable and curable, it continues to be a significant cause of morbidity and mortality, particularly in tropical and subtropical regions[1]. Various control measures including vector control and antimalarial chemotherapy have been employed to reduce its burden[2]. Artemisinin-based combination therapies (ACTs) are currently the WHO-recommended first-line treatments for uncomplicated malaria[3]. However, concerns remain about the cardiotoxic effects of some antimalarial drugs, particularly with increased use and potential drug resistance requiring more potent combinations[4,5].

The isolated perfused frog heart was first developed by Carl Ludwig and Elias Cyon in 1866[6]. This innovation laid the foundation for later mammalian heart perfusion systems devised by H. Newell Martin in 1883 and Oscar Langendorff in 1895[6]. The frog heart model remains valuable for pharmacological studies. For instance, a negative inotropic response was observed when total alkaloidal salts from *Moringa oleifera* leaf were applied to an isolated frog heart[7]. Similarly, atropine's reversal of

acetylcholine-induced bradycardia and enhancement of contraction amplitude were demonstrated using the in-situ frog heart preparation[8].

Knight et al. adapted the Langendorff method to demonstrate cardiac mechanical and electrical events using a frog heart rather than a mammalian heart[9]. An advantage of the frog heart preparation is that it can be maintained at room temperature without supplemental oxygenation. The frog heart can remain viable for twelve to twenty-four hours when perfused with solutions like Ringer's or sucrose[6]. In pithed frog heart preparations, the absence of influence from the autonomic nervous system, endocrine factors, and systemic ions enhances the model's utility for cardiovascular pharmacological investigations[10].

Understanding the cardiac effects of these drugs is essential, particularly in vulnerable populations. Chloroquine and quinine have been associated with QT prolongation and arrhythmias[5]. The in-situ frog heart model provides a simple yet effective experimental setup to assess cardiac responses to drugs, excluding systemic and autonomic influences. This study investigates the cardiotonic effects of chloroquine, artemether-lumefantrine, and artesunate using this model.

METHODOLOGY

Study site

The study was conducted in the Department of Pharmacology and Therapeutics, Faculty of Basic Medical Science, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Equipment

The materials and equipment utilized for this research included: 5 mL and 2 mL needles and syringes, glass bottles, tissue paper, conform gloves, giving set, retort stand, slab, tray, stop clock, standby generator and petrol, Normal Saline, Ringer's solution, dissecting set, clip with standard weight, weighing balance, stabilizer, external drive for data backup, force transducer, and a laptop computer.

Calibration

The software employed in this study measured readings of the transducers in millivolt (mV). Consequently, calibration was performed to establish the millivolt equivalent of one gram-force (1 gF).

This was achieved by defining and determining the gram-force through the use of an ultra-sensitive weighing balance to weigh two paper clips, thereby correlating the measured weight with its corresponding millivolt value.

The weight of 2 paper clips = 2.09 g = 2.09-gram force (1gram = 1gram force)

On suspending the 2 clips with 2.09gF, 0.003volts was produced.

Therefore, if 0.003volts is produced by 2.09gF, 1gF will produce x volts

$$x = \frac{0.003}{2.09} = 0.0014354\ volts$$

1 gF = 1.4354 mV

Cardiac impulse conversion

Experimental animals

The experimental animals used in this study were frogs (*Rana temporaria*), with an average weight of approximately 150 g. They were sourced from the laboratory of the Department of Physiology, University of Ibadan, Ibadan, Nigeria.

Preparation of Amphibian Cardiac Model

The frog was pithed and positioned dorsally. A midline thoracic incision was made to expose the heart. A clip was secured to the apex of the heart and connected to the force transducer via a thread. The set up was then adjusted to ensure appropriate tension, and the system was allowed to stabilize for 60 minutes. During the stabilization period, Ringer's solution was applied at 15-minute intervals to maintain cardiac moisture. The experiment commenced immediately following the stabilization period. Each experiment considered the changes in the baseline readings of each toad. Between toad comparisons were not used as each baseline was not the same.

Fig 1: Photograph of the frog heart preparation during one of the experiments

Drugs

The test drugs (chloroquine, artesunate, and artemether/Lumefantrine) used were oral formulations of the following antimalarial purchased at a popular Community Pharmacy opposite University of Ibadan: the authenticities of the drugs were validated using the scratchpads provided by the manufacturing companies.

Tablet formulation and dose determination

Whole tablets were initially crushed and dissolved in normal saline to prepare stock solutions or suspensions. Two doses of the test drugs were evaluated; therapeutic dose (TD) equivalent to the therapeutic dose in humans (adults) and a supratherapeutic dose (SD) equivalent to ten times the therapeutic dose. From the stock, the required therapeutic dose was obtained through serial dilutions. The therapeutic dose was calculated using equations explained below. To obtain the supratherapeutic dose, a solution ten times the strength of the therapeutic dose was prepared.

Drug dosing and calculation

The formula shown below was used for the calculation of the required therapeutic dose for the test drugs:

$$\text{Therapeutic dose} = \frac{\text{therapeutic dose in humans (in mg/kg/day) x weight of the frog (in grams)}}{1000}$$

- Supratherapeutic dose (SD) = 10 x the therapeutic dose (for instance for chloroquine = 10 x 1.5mg = 15mg). Thus, the SD was prepared such that the dose, 15mg, was dissolved in 5mL normal saline

Dose Calculation of Chloroquine Tablet

The chloroquine tablet used for the project contained 250 mg of the active ingredient. (Chloroquine Phosphate Tablets BP 250 mg: Manufacturer, Emzor Pharmaceutical Industries Ltd., Lagos, Nigeria. Batch No. ALDS 170923; Manufacturing Date, February, 2017; Expiry Date, January 2017). Given at a dose of 10 mg/kg, a stock solution was prepared by dissolving the entire 250 mg in 25 mL of normal saline, giving a final concentration of 10 mg/mL, using the formula below:

$$Required\ therapeutic\ dose = \frac{normal\ therapeutic\ dose\ (in\ mg/kg/day)\ x\ weight\ of\ the\ frog\ (in\ grams)}{1{,}000}$$

Therapeutic dose of chloroquine = 10 mg/kg
Weight of frog = 88 g
Required therapeutic dose for the frog is 10 x 88/1000 = 0.88 mg
From the stock solution (10 mg/mL), a 1 mL aliquot containing 10 mg of chloroquine was diluted with 9mL of normal saline. This gave a secondary solution with a final concentration of 1mg/mL of the solution contains 1 mg of chloroquine, the volume (X) required to obtain 0.88 mg was determined using the equation:

$$X = \frac{0.88\ x\ 1}{1} = 0.88\ mL$$

The same approach was used to determine the supratherapeutic dose, which started with the preparation of a stock solution of chloroquine containing 100mg/mL.

Dose Calculation of Artemether-lumefantrine

The amount of artemether-lumefantrine in the tablet was 80/480mg (Artemether/Lumefantrine Tablets 80 mg/480 mg (Lonart® DS): Manufacturer, Bliss GVS Pharma Ltd., Mumbai, India. Batch No. ALDS 170924; Manufacturing Date, August, 2017; Expiry Date, July, 2017). The dose calculation was based on the therapeutic dose of artemether, 4mg/kg. A tablet was dissolved in 8mL of normal saline to give 10mg/mL

$$Required\ therapeutic\ dose = \frac{normal\ therapeutic\ dose\ (in\ mg/kg/day)\ x\ weight\ of\ the\ frog\ (in\ grams)}{1{,}000}$$

Therapeutic dose of artemether = 4mg/kg
Weight of frog used = 69g

$$Required\ dose\ = \frac{4\ x\ 69}{1{,}000} =\ 0.276\ mg$$

From concentration of 10mg/mL, 1 mL containing 10mg of artemether was diluted with 9 mL of normal saline. This gave the solution with concentration of 1mg/mL artemether $(10\ mg \div 10\ mL = 1\ mg/mL)$
The volume that will contain the required therapeutic dose (therapeutic volume) was calculated as follows:
If 1mL contained 1mg, then 0.276mg will be contained in XmL.

$$X\ = \frac{0.276\ x\ 1}{1} =\ 0.276\ mL$$

Thus, the volume of concentration that gave the therapeutic dose was 0.276mL
The volume required for supratherapeutic dose (SD) = 10 x the required therapeutic dose. SD for artemether-lumefantrine tablet was $10 \times 0.276\ mL = 2.76\ mL$

Dose Calculation for Artesunate

The amount of artesunate in artesunate tablet was 2x500mg and the therapeutic dose was 4mg/kg. (Artesunate Tablets 50 mg. Manufacturer, Guilin Pharmaceutical Co., Ltd., Guangxi, China. Batch No. AS 170923; Manufacturing Date, September, 2017; Expiry Date, August, 2017). The 100mg tablet was dissolved in 10 mL normal saline to give 10mg/mL
$(100\ mg \div 10mL\ = 10\ mg/mL)$

$$Required\ therapeutic\ dose\ = \frac{normal\ therapeutic\ dose\ (in\ mg/kg/day)\ x\ weight\ of\ the\ frog\ \ (in\ grams)}{1{,}000}$$

Normal therapeutic dose = 4mg/kg
Weight of frog used = 84g

$$Required\ therapeutic\ dose\ = \frac{4\ x\ 84}{1{,}000} = 0.338\ mg$$

From 10mg/mL, 1 mL containing 10mg of artesunate was diluted with 9 mL of normal saline. This gave artesunate solution with concentration of 1mg/mL (10mg/10mL)
The volume that will contain the required therapeutic dose was calculated as follow:
If 1mL contained 1mg, then 0.336mg will be contained in XmL.
X = (0.336 x 1)/1 = 0.336 mL
Thus, the therapeutic dose was approximately 0.4 mL
Volume for a supratherapeutic dose (SD) = 10 x the required therapeutic dose. SD for Artesunate:
$10 \times 0.336\ mL = 3.36\ mL \sim 4\ mL$

Drug administration

For the administration of each prepared drug concentration, 5 mL of the respective solution containing the calculated doses was used to perfuse the suspended frog heart. The perfusion was carried out slowly delivering the solution over a 20-second period using a 5 mL syringe, allowing direct contact with the cardiac tissue. Following drug administration, a washout procedure was implemented using 25 mL of Ringer's lactate solution. This was repeated three times over a 10-minute interval to ensure adequate removal of the drug from the cardiac tissue before subsequent doses were administered.

Time points of drug administration

The drug administration commenced after a stable baseline heart tracing was achieved. Drug administration was such that the control solution of normal saline was administered first, followed by the lowest concentration of the drug and

then the supratherapeutic dose. The drug was allowed to act for 2 minutes after administration for each concentration before washout. Washout was done three times after every drug administration.

Measured parameters

The study assessed the following cardiac parameters:

1) Heart rate (beats per minute: to evaluate chronotropic effects.

2) Force of contraction: to determine changes in myocardial contractility.

3) Gram force of cardiac impulse (gF): calculated using the conversion formula described above.

Interpretation of results

An upward deviation in millivolts (mV) readings from the established baseline indicated an increase in the force of heart contraction, while a reduction in mV corresponded to a decrease in myocardial contractile force. These changes were quantitatively assessed using the conversion factor: $1gf = 1.4354\ mV$

The heart rate was the number of cycles counted per minute.

RESULTS

Changes in heart rate

Three frogs were pithed and *in-situ* heart preparations were mounted for the evaluation of chloroquine, artemether-lumefantrine and artesunate respectively for the measurement of heart rate and amplitude (fig. 1). The baseline heart rate for chloroquine was 75 beats per minute (Fig 2). This decreased as the dose of chloroquine increased. The heart rate decreased to 66 beats per minute at the therapeutic dose and to 60 beats per minute at 10X the therapeutic dose (supratherapeutic dose). For artemether-lumefantrine, baseline heart rate was 39 beats per minute. There was no difference between the baseline heart rate and the heart rate at therapeutic dose. However, the heart rate decreased to 36 beats per minute at 10X the therapeutic dose. The baseline heart rate for artesunate was 36 beats per minute, which increased as the dose of artesunate increased. There was an increase from the baseline heart rate to 51 beats per minute at the therapeutic dose and to 42 beats per minute at 10X the therapeutic dose.

Changes in amplitude

Table 1 is a comprehensive presentation of the results obtained during the project. The baseline amplitude of contraction for chloroquine was 3.94 mV. Chloroquine caused a decrease in amplitude of contraction at therapeutic dose to 3.71 mV but increased the amplitude of contraction to 3.96 mV at the 10X its therapeutic dose. The baseline amplitude of contraction for artemether-lumefantrine was 6.28 mV. The therapeutic dose and the 10X the therapeutic dose of artemether-lumefantrine both depressed the amplitude of contraction to 6.17 mV and 6.16 mV respectively. The baseline amplitude of contraction for artesunate was 16.85 mV. Artesunate decreased the amplitude of contraction from the baseline to 13.78 mV at therapeutic dose and to 14.05mV at 10X the therapeutic dose.

Changes in cardiac impulse (force of contraction, gram force)

Using the conversion factor described under the methodology section, one-gram force of contraction of the frog heart is equal to 1.44 mV. The baseline gram force of contraction for chloroquine was 2.7gF. A decrease in gram force of cardiac contraction to 2.6gF was observed for chloroquine at therapeutic dose while the gram force of contraction at 10X its therapeutic dose increased to 2.8gF. The gram force of contraction for artemether-lumefantrine at the baseline was 4.4 gF while the therapeutic dose and 10X the therapeutic dose of artemether-lumefantrine both decreased the contraction force to 4.3 gF. The baseline gram force of contraction for artesunate was 11.7 gF. At therapeutic dose, artesunate decreased the heart contraction from the baseline to 9.6 gF while 10X therapeutic dose decreased it to 9.8 gF.

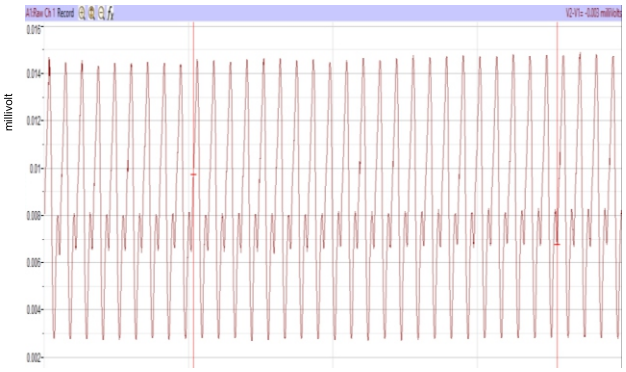

Fig. 2: Baseline tracing for chloroquine

Table 1: Table of results showing the effect of chloroquine, artemether/lumefantrine and artesunate on the heart rate and force of contraction.

	Parameters	Chloroquine	Artemether/lumefantrine	Artesunate
Baseline	Heart rate (bpm)	75	39	36
	Max (millivolts)	4.23	7.88	14.88
	Min (millivolts)	0.29	1.59	-1.97
	Amplitude (millivolts)	3.94	6.28	16.85
	Force of contraction (gF)	2.7	4.4	11.7
Therapeutic Dose	Heart rate (bpm)	66	39	51
	Max (millivolts)	4.07	7.63	13.46
	Min (millivolts)	0.35	1.46	-0.32
	Amplitude (millivolts)	3.71	6.17	13.78
	Force of contraction (gF)	2.6	4.3	9.60
Supratherapeutic Dose - 10X Therapeutic Dose	Heart rate (bpm)	60	36	42
	Max (millivolts)	4.15	7.80	14.59
	Min (millivolts)	0.19	1.64	0.54
	Amplitude (millivolts)	3.96	6.16	14.05
	Force of contraction (gF)	2.8	4.3	9.8

$$Amplitude\ in\ millivolts\ =\ Max - Min$$

$$Gram\ force\ of\ contraction\ of\ the\ heart = \frac{Amplitude}{1.4354\ mV}$$

DISCUSSION

This study examined the cardiac effects of chloroquine, artemether-lumefantrine, and artesunate using the in-situ frog heart preparation. The model provided a controlled environment to assess direct drug effects on myocardial rate and contractility, free from systemic or autonomic influences. The findings highlight distinct chronotropic and inotropic profiles for each agent, offering insights into their relative cardiotoxic potentials.

Chloroquine demonstrated a clear negative chronotropic effect, with heart rate reductions of 12% at therapeutic and 20% at supratherapeutic doses. These results corroborate earlier studies linking chloroquine with bradycardia and QT prolongation[11,12]. Mechanistically, chloroquine blocks cardiac sodium and potassium channels, delaying depolarization and repolarization, which predisposes patients to conduction disturbances and arrhythmias (13). The observed increase in contractile force at the higher dose is likely explained by the Frank-Starling mechanism, wherein prolonged diastolic filling enhances stroke volume[14,15].

The cardiotoxic potential of chloroquine has long been recognized in both acute poisoning and chronic therapy. Clinical cases describe hypotension, arrhythmias, and cardiogenic shock in overdoses, with mortality linked to plasma concentrations[12, 16]. Its cardiotoxicity has gained renewed attention during the COVID-19 pandemic, where chloroquine and hydroxychloroquine were investigated as repurposed therapies but later restricted due to safety concerns[17]. Our findings reinforce that even experimental doses can induce significant changes in cardiac physiology.

Artemether-lumefantrine showed a relatively safe cardiac profile, with negligible effects on heart rate at therapeutic levels and only modest reductions at higher concentrations. This aligns with human studies reporting minimal impact on QT interval duration[18]. The combination's tolerability is an important factor in its designation as the WHO first-line therapy for uncomplicated malaria[19]. Its safety in special populations, including children and pregnant women, further supports its continued global use[20].

The pharmacological basis of artemether-lumefantrine's cardiac safety may relate to lumefantrine's long half-life and stable plasma levels, which reduce the risk of electrophysiological disturbances[21]. Although some in vitro studies have suggested minor interactions with cardiac ion channels, clinically significant arrhythmias are rare[22]. The present findings are therefore consistent with its widely

acknowledged safety record.

Artesunate presented a more complex profile, producing a strong positive chronotropic effect but a negative inotropic response. At therapeutic doses, heart rate increased by over 40%, whereas contractile force decreased by nearly 18%. Such divergent effects may be due to sympathetic stimulation or reflex tachycardia, resulting from vasodilatory properties that reduce afterload[23]. The reduction in contractility could also reflect limited calcium handling at the myocardial level, though further mechanistic studies are warranted.

These findings raise concerns about artesunate use in patients with pre-existing cardiac compromise. While artesunate is generally regarded as safe and does not prolong QT intervals in clinical settings[24], the possibility of increased heart rate without compensatory contractility may be detrimental in patients with heart failure or ischemic disease. Our data suggest that artesunate's cardiovascular effects may warrant closer monitoring in such populations. Further studies into this observation are required.

The frog heart model, although simple, has demonstrated utility in capturing drug-induced cardiac effects consistent with human physiology. Its advantages include exclusion of confounding systemic factors, reproducibility, and low maintenance requirements[25]. However, extrapolation to human outcomes must remain cautious, as amphibian myocardium differs in calcium handling and action potential morphology from mammalian hearts. Nevertheless, the consistency of our results with clinical reports underscores its predictive value.

Taken together, our findings highlight a spectrum of cardiac effects among commonly used antimalarials. Chloroquine poses risk through bradycardia and conduction abnormalities, artemether-lumefantrine maintains a favorable cardiac safety profile, and artesunate demonstrates dose-dependent chronotropic and inotropic divergence. These results provide a pharmacological rationale for vigilance in antimalarial drug deployment, especially as combination therapies and higher-dose regimens are explored in the fight against antimalarial drug resistance.

CONCLUSION

This study demonstrates distinct cardiac profiles for three widely used antimalarial drugs. Chloroquine produced significant, dose-dependent bradycardia and conduction abnormalities consistent with its established cardiotoxicity. Artemether-lumefantrine exhibited a favorable cardiac safety profile, with minimal chronotropic and inotropic effects even at supratherapeutic levels, reinforcing its role as a first-line therapy. Artesunate produced a paradoxical effect, markedly increasing heart rate while reducing contractile force, a profile that warrants further exploration to clarify its implications in vulnerable patients.

The in-situ frog heart model proved valuable in capturing these pharmacodynamic effects, aligning well with clinical data. These findings emphasize the need for ongoing pharmacovigilance in malaria treatment, particularly as drug resistance and combination therapies evolve. Rational drug selection should balance efficacy with cardiac safety, especially in patients with pre-existing cardiovascular conditions.

REFERENCES

1. World Health Organization. World malaria report 2023. Geneva: WHO; 2023.
2. Renslo AR. Antimalarial drug discovery: from quinine to the dream of eradication. ACS Med Chem Lett. 2013;4(12):1126–8.
3. White NJ. Antimalarial drug resistance. J Clin Invest. 2004;113(8):1084–92.
4. Thanacoody RH. Quinine and chloroquine. Medicine (Abingdon). 2016;44(10):622–4.
5. Marrelli MT, Brotto M. The effect of malaria and anti-malarial drugs on skeletal and cardiac muscles. Malar J. 2016;15(1):524.
6. Zimmer HG. The isolated perfused heart and its pioneers. Physiology. 1998;13(4):203–10.
7. Dangi SY, Jolly CI, Narayanan S. Antihypertensive activity of the total alkaloids from the leaves of Moringa oleifera. Pharm Biol. 2002;40(2):144–8.
8. Kothapalli J. Effect of atropine on cardiac rhythm of frog's heart. Int J Adv Res. 2017;5(4):123–6.
9. Knight VA, Richardson DR, Makoba B. Use of frog ventricle to examine mechanical and electrical activity of heart. Am J Physiol. 1989;256(6 Pt 2):S9–S14.
10. Olejníčková V, Nováková M, Provazník I. Isolated heart models: cardiovascular system studies and technological advances. Med Biol Eng Comput. 2015;53(4):547–56.
11. Sowunmi A, Salako LA, Walker O. Cardiovascular effects of chloroquine in children with malaria. Trans R Soc Trop Med Hyg. 1999;93(3):320–3.
12. Thanacoody RH. Extracellular and intracellular consequences of chloroquine poisoning. Toxicol

Rev. 2016;35(3):185–92.
13. White NJ. Cardiotoxicity of antimalarial drugs. Lancet Infect Dis. 2007;7(8):549–58.
14. Sequeira V, van der Velden J. Historical perspective on heart function: the Frank–Starling law. Biophys Rev. 2015;7(4):421–47.
15. Zimmer HG. The role of mechanical stretch in cardiac hypertrophy. Mol Cell Biochem. 2019;241(1–2):1–11.
16. Phillips-Howard PA, ter Kuile FO. CNS adverse events associated with antimalarial drugs. Drug Saf. 1995;12(6):370–83.
17. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm. 2020;17(9):1425–33.
18. Degen P, Juillard P, de Riedmatten M. Assessment of cardiac safety during treatment with artemether–lumefantrine in healthy volunteers. Clin Drug Investig. 2002;22(3):169–79.
19. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva: WHO; 2015.
20. Manyando C, Njunju EM, D'Alessandro U, Van Geertruyden JP. Safety and efficacy of artemether–lumefantrine in pregnancy: a systematic review. Malar J. 2012;11:141.
21. Ashley EA, Stepniewska K, Lindegardh N, et al. Population pharmacokinetic assessment of a new regimen of artemether-lumefantrine in patients with uncomplicated falciparum malaria. Antimicrob Agents Chemother. 2007;51(12):4090–7.
22. Borsini F, Crumb W, Pace S, et al. In vitro cardiovascular effects of dihydroartemisinin–piperaquine compared with other antimalarials. Antimicrob Agents Chemother. 2012;56(6):3261–70.
23. Gordi T, Lepist EI. Artemisinin derivatives: toxic for laboratory animals, safe for humans? Toxicol Lett. 2004;147(2):99–107.
24. Maude RJ, Plewes K, Faiz MA, et al. Does artesunate prolong the electrocardiograph QT interval in patients with severe malaria? Am J Trop Med Hyg. 2009;80(1):126–32.
25. Olejníčková V, Nováková M, Provazník I. Isolated heart models: cardiovascular system studies and technological advances. Med Biol Eng Comput. 2015;53(4):547–56.