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LETTER

Dosing Time of Day Impacts the Safety of Antiarrhythmic Drugs in a Computational Model of Cardiac Electrophysiology

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Abstract Circadian clocks regulate many aspects of human physiology, including cardiovascular function and drug metabolism. Administering drugs at optimal times of the day may enhance effectiveness and reduce side effects. Certain cardiac antiarrhythmic drugs have been withdrawn from the market due to unexpected proarrhythmic effects such as fatal Torsade de Pointes (TdP) ventricular tachycardia. The Comprehensive in vitro Proarrhythmia Assay (CiPA) is a recent global initiative to create guidelines for the assessment of drug-induced arrhythmias that recommends a central role for computational modeling of ion channels and *in silico* evaluation of compounds for TdP risk. We simulated circadian regulation of cardiac excitability and explored how dosing time of day affects TdP risk for 11 drugs previously classified into risk categories by CiPA. The model predicts that a high-risk drug taken at the most optimal time of day may actually be safer than a low-risk drug taken at the least optimal time of day. Based on these proof-of-concept results, we advocate for the incorporation of circadian clock modeling into the CiPA paradigm for assessing drug-induced TdP risk. Since cardiotoxicity is the leading cause of drug discontinuation, modeling cardiac-related chronopharmacology has significant potential to improve therapeutic outcomes.

Keywords circadian rhythms, cardiac electrophysiology, computational modeling, ion channels, Comprehensive in vitro Proarrhythmia Assay (CiPA), chronopharmacology

INTRODUCTION

Circadian (approximately 24-h) rhythms influence the activity of various physiological processes, such as liver function and renal clearance, which can impact how drugs are processed in the body. The body's response to a drug can be influenced by factors such as the expression of drug-metabolizing enzymes, receptor sensitivity, and the timing of sleep-wake cycles (Bicker et al., 2020; Gachon and Firsov, 2011; Holst et al., 2016; Lu et al., 2020). Drug metabolism, absorption, and distribution all exhibit circadian variations (Baraldo, 2008; Gachon and Firsov, 2011; Paschos and FitzGerald, 2010; Smolensky et al., 2007). Furthermore, over 50 of the 100 best-selling drugs in the United States target the product of genes that exhibit circadian rhythms in expression (Zhang et al., 2014). For example, circadian oscillations are observed in the expression of genes that encode cardiac ion channels targeted by heart medications

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(Ruben et al., 2018). Therefore, taking a cardiovascular drug at the right time of day may maximize its effectiveness, minimize side effects, and improve overall therapeutic outcomes. Understanding the circadian variations in drug response and identifying the optimal time of day for drug intake can enhance a drug's safety and efficacy. This knowledge is particularly important for medications with short half-lives and narrow therapeutic windows, or those that interact with biological pathways in a strongly time-dependent manner (Anwar and White, 1998; Dallmann et al., 2014; Erkekoglu and Baydar, 2012; Grimm et al., 2009; Smolensky et al., 2007).

Adverse cardiac effects are the leading cause of drug development discontinuation (Ferdinandy et al., 2019; Ruben et al., 2019). Several antiarrhythmic drugs have been withdrawn from the market due to unexpected proarrhythmic effects, including fatal Torsade de Pointes (TdP) ventricular tachycardia (Dutta et al., 2017b; Gintant, 2008). Drug-induced TdP is associated with prolonged repolarization duration and may result from the unintended side effect of blocking Kv11.1 human Ether-a-go-go (hERG) channels that conduct rapidly activating delayed rectifier potassium current (I_{Kr}). Mandatory in vitro screening of new pharmaceuticals for I_{Kr} block has been effective in reducing incidence of drug-related TdP (McMillan et al., 2017). However, since I_{Kr} block is not a sensitive predictor of TdP risk, the development of some safe drugs may be needlessly discontinued by this screening process (Sager et al., 2014).

To address this issue, the Comprehensive in vitro Proarrhtyhmia Assay (CiPA) regulatory framework evaluates drug-induced TdP risk through a combination of in vitro measurements and *in silico* modeling of the effects a drug has on many different cardiac ionic currents (Colatsky et al., 2016; Fermini et al., 2016; Li et al., 2020). During the development and validation of CiPA, 28 drugs were classified into high, medium, and low clinical TdP risk categories by a group of cardiologists, pharmacologists, and electrophysiologists. In this paper, we focused on 11 of these drugs and used the O'Hara-Rudy (ORd) model of ventricular myocytes—the base model chosen for the *in silico* component of CiPA—to investigate how circadian regulation of cardiac ion channels affects drug-induced TdP risk (O'Hara et al., 2011).

In particular, we utilized a version of the ORd model with dynamic I_{Kr} to enable the modeling of interactions between drugs, I_{Kr}, and other ion channels (Li et al., 2017). We simulated circadian variation in cardiac excitability based on known rhythms in cardiac ion channel expression and used qNet, a well-established metric for TdP risk defined as the net charge from the initiation to the conclusion of a simulated beat, to assess drug safety.

METHODS

We incorporated circadian variation in the maximal conductance of 4 ionic currents into the optimized I_{Kr}-Dynamic ORd Model (Dutta et al., 2017a): sodium (I_{Na}), L-type calcium (I_{CaL}), rapid delayed rectifier potassium (I_{Kr}), and transient outward potassium (I_{to}). For each of these currents, we employed a sinusoidal waveform for the maximal conductance parameter as shown in equations (1)-(4), with peak and trough times selected based on circadian rhythms in the abundance of the ion channel proteins SCN5A (Tikhomirov et al., 2024), CACNA1C (Chen et al., 2016), KCNH2 (Tikhomirov et al., 2024), and Kv4.2 (Yamashita et al., 2003), respectively.

$$G_{Na} = G_{Na_{\min}} + \frac{G_{Na_{\max}} - G_{Na_{\min}}}{2}\left(\sin\left(\frac{-2\pi(t-28)}{24}\right)+1\right) \quad (1)$$

$$P_{Ca} = P_{Ca_{\min}} + \frac{P_{Ca_{\max}} - P_{Ca_{\min}}}{2}\left(\sin\left(\frac{2\pi(t+3)}{24}\right)+1\right) \quad (2)$$

$$G_{Kr} = G_{Kr_{\min}} + \frac{G_{Kr_{\max}} - G_{Kr_{\min}}}{2}\left(\sin\left(\frac{2\pi(t-6)}{24}\right)+1\right) \quad (3)$$

$$G_{to} = G_{to_{\min}} + \frac{G_{to_{\max}} - G_{to_{\min}}}{2}\left(\sin\left(\frac{-2\pi t}{24}\right)+1\right). \quad (4)$$

Figure 1 shows a comparison of the experimental measurements of protein abundance and our simulated conductances for each current. Protein measurements are from experiments on nocturnal rodent species, with zeitgeber time (ZT) 12 corresponding to the start of the dark/active phase. Circadian rhythms have been observed in the mRNA levels of *Scn5a*, the gene encoding a sodium channel subunit underlying I_{Na} (Schroder et al., 2013; Tikhomirov et al., 2024). Although Tikhomirov et al. (2024) did not observe a circadian rhythm in abundance of the corresponding protein SCN5A, they did observe that protein levels were significantly higher at ZT0 than ZT12 (Figure 1a). They then performed voltage-clamp experiments and found that the peak I_{Na} current was approximately 1.7 times higher at ZT0 than ZT12. Chen et al. (2016) observed a circadian rhythm in the protein abundance of CACNA1C, a calcium channel protein underlying I_{CaL} (Figure 1b). They also performed voltage-clamp experiments and found that the peak I_{CaL} current was approximately 1.4 times higher at ZT3 than ZT15. Tikhomirov et al. (2024)

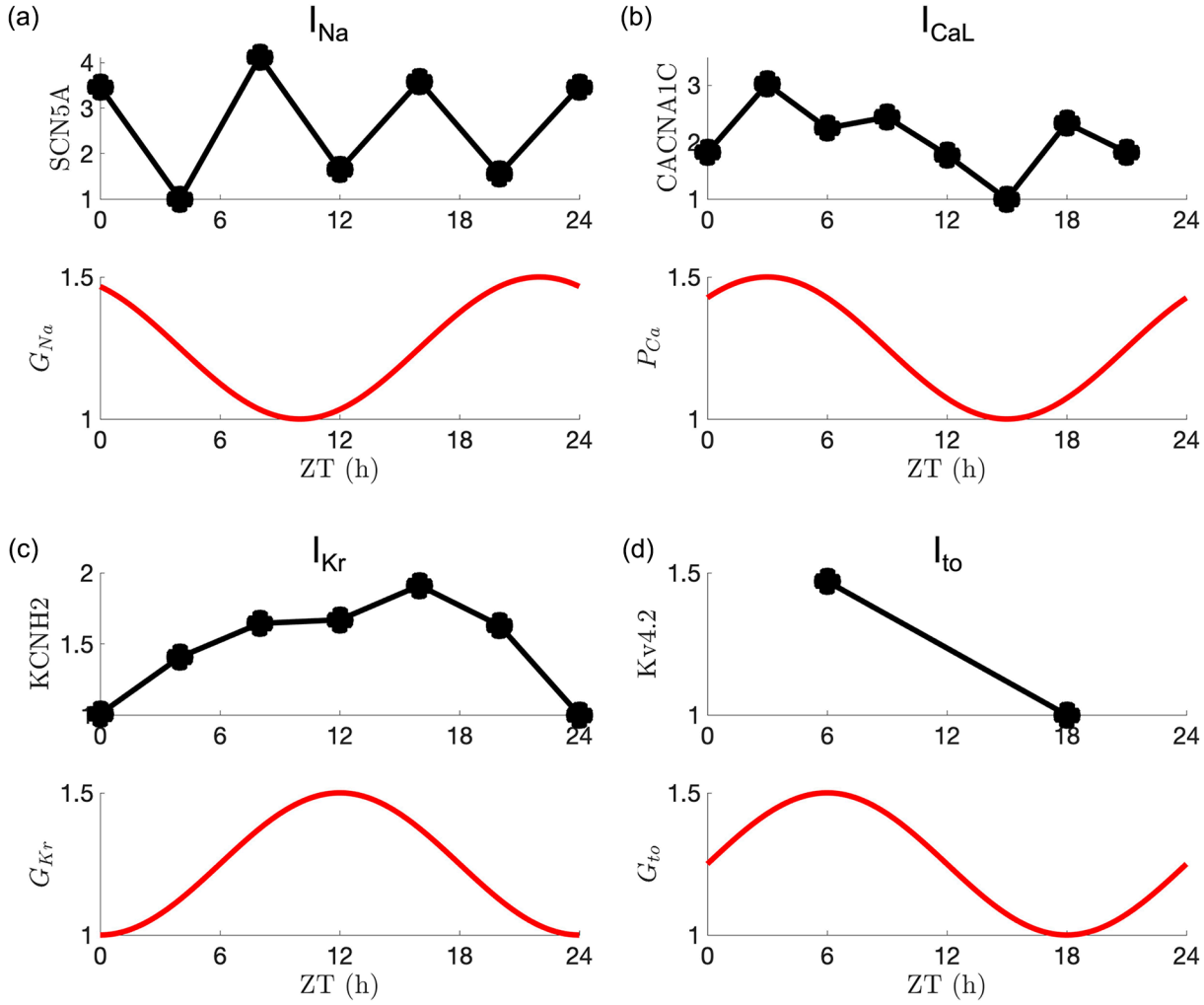

Figure 1. Experimental measurements of ion channel protein abundance and simulated ion channel conductances. ZT12 corresponds to the start of the dark/active phase. (a) SCNA protein abundance measured by Tikhomirov et al. (2024; black) and simulated I_{Na} conductance (red). (b) CACNA1C protein abundance measured by Chen et al. (2016; black) and simulated I_{CaL} permeability (red). (c) KCNH2 protein abundance measured by Tikhomirov et al. (2024; black) and simulated I_{Kr} conductance (red). (d) Kv4.2 protein abundance measured by Yamashita et al. (2003; black) and simulated I_{to} conductance (red).

observed a circadian rhythm in the protein abundance of KCNH2, a potassium channel subunit underlying I_{Kr} (Figure 1c). They also performed voltage-clamp experiments and found that I_{Kr} current was 1.5 times higher at ZT12 than ZT0. Finally, Yamashita et al. (2003) observed a circadian rhythm in the mRNA levels of Kv4.2, a potassium channel underlying I_{to}. They measured abundance of the corresponding Kv4.2 protein and found significantly higher levels at ZT6 than ZT18 (Figure 1d). Yamashita et al. also performed voltage-clamp experiments and found that peak I_{to} current was 1.4 times higher at ZT6 than ZT18.

Since the peak current was approximately 1.5 times higher at the circadian zenith than the circadian nadir for all 4 currents, we simulated a 1.5-fold difference between G_{max} and G_{min} for each current (except for I_{CaL}, in which case we simulated a 1.5-fold difference between $P_{Ca_{max}}$ and $P_{Ca_{min}}$).

The optimized I_{Kr} dynamic model incorporates the dynamics of antiarrhythmic drug binding. Our analysis involved the following 11 drugs: bepridil, chlorpromazine, cisapride, dofetilide, diltiazem, mexiletine, ondansetron, ranolazine, sotalol, terfenadine, and verapamil. Simulations were initiated from control steady-state conditions, employing a cycle length of 2000 ms and a stimulus of −80 μA/μF for 0.5 ms. For each drug analyzed, we continued pacing in 1000-beat increments until a new steady state was reached under the influence of the drug. The last two

beats were monitored to detect alternans and the presence of early afterdepolarizations (EADs), defined as exhibiting a positive derivative during the repolarization phase of the action potential (AP). We utilized the drug-I_{Kr} binding kinetic parameters from Dutta et al. (2017a), along with drug IC50/Hill coefficients from Dutta et al. (2017a) for the following currents: I_{Na}, I_{NaL} (late sodium), I_{CaL}, I_{K1} (inwardly rectifier potassium), I_{Ks} (slow rectifier potassium), and I_{to}. Simulations were conducted across a spectrum of drug concentrations, ranging from 0.5× to 25× free maximum plasma clinical drug exposures (C_{max}). All the data presented in the "Results" section corresponds to 4× C_{max}. We calculated the metric qNet as outlined in Dutta et al. (2017a), determined by the net charge encompassed by (the integral or area under the curve of) the net current (I_{Net}) from the initiation to the conclusion of the simulated beat, where $I_{Net} = I_{CaL} + I_{NaL} + I_{Kr} + I_{Ks} + I_{K1} + I_{to}$. The currents constituting I_{Net} in our investigation play a pivotal role in modulating arrhythmic risk and have been selected based on input from scientists in pharmaceutical companies and safety pharmacology experts as the primary currents of interest within the CiPA paradigm (Fermini et al., 2016). Several studies have shown qNet to be an accurate predictor of TdP risk (Gaur et al., 2020; Parikh et al., 2019; Qauli et al., 2023). Dutta et al. (2017a) investigated the physiological significance of qNet using concepts from dynamical systems theory, and found that this capability arises from qNet's correlation with the system's ability to maintain repolarization robustness in response to external perturbations, such as a decrease in hERG channel density or a reduction in I_{Kr} maximum conductance.

We evaluated the influence of circadian variations in ionic currents on the drug's safety by calculating qNet with daily drug administration at 24 different times of day, from ZT0 to ZT24 in hourly intervals (ZT0 corresponds to the start of the light period and ZT12 to the start of the dark period). The optimal timing for drug intake was identified as the time of day with maximal qNet. We also calculated relative qNet, defined as the difference between qNet in the presence and absence of a drug, to isolate the effect that time of day has on drug-induced TdP risk:

$$\begin{aligned}\text{qNet} &= \int_0^{\text{cycle length}} I_{Net}\, dt \\ &= \int_0^{\text{cycle length}} \left(I_{CaL} + I_{NaL} + I_{Kr} + I_{Ks} + I_{K1} + I_{to}\right) dt \\ \text{relative qNet} &= \left(\text{qNet with drug}\right) \\ &\quad - \left(\text{qNet without drug}\right).\end{aligned}$$

Since Li et al. (2017) utilized endocardial cells when formulating the dynamic hERG-binding ORd model, we chose to focus on this cell type in our study. However, we also repeated all our simulations using epicardial ORd parameters, and obtained qualitatively similar results to those presented here for endocardial cells.

RESULTS

We assessed the interaction of circadian rhythms in cardiac excitability and 11 cardiac antiarrhythmic drugs by simulating daily drug administration at 24 different times of day. For each dosing time, we calculated qNet, a metric for evaluating drug-induced modifications to the net charge carried by ionic currents during the AP (Dutta et al., 2017a). This metric has been used to categorize CiPA training drugs into 3 levels of TdP risk (low, medium, and high) across different conditions, with a higher qNet corresponding to lower TdP risk.

The effect that dosing time of day has on qNet is illustrated for endocardial cells in Figure 2a and for epicardial cells in Figure 2b. Drugs previously classified as low, medium, and high TdP risk in the absence of circadian variation are shown in various shades of green, blue, and red, respectively. The overall pattern of circadian variation is similar for both cell types. Thus, we chose to focus on just one cell type, endocardial, for the remainder of the paper. The qNet value for 8 out of the 11 drugs (all except for the low-risk drugs diltiazem, mexiletine, and verapamil) exhibited more than a 2-fold difference in qNet depending on the time of day the drug was administered, with 2 high-risk drugs (bepridil and dofetilide) exhibiting a more than 3-fold difference. Figure 2c and 2d shows that 2 low-risk drugs (verapamil and ranolazine) actually have a higher TdP risk (lower qNet value) when taken at their least optimal time of day (ZT1 and ZT2, respectively) than the 3 high-risk drugs (bepridil, dofetilide, and sotalol) when taken at their most optimal time of day (ZT15). Indeed, when taken at ZT2, ranolazine has a higher TdP risk than sotalol taken anywhere from ZT9 to ZT20.

The membrane potential and ionic current traces during an AP for the low-risk drug ranolazine administered at its most (ZT15) and least (ZT2) optimal times of day are shown in Figure 3. The AP duration (APD) is extended at ZT2 relative to ZT15 (see voltage traces), a feature typically associated with EADs and the potential for TdPs. At ZT2, the I_{CaL}, I_{Ks}, and I_{to} currents have larger peak amplitudes, whereas the I_{Kr} current has a smaller peak amplitude but a prolonged duration. I_{NaL} and I_{K1} have similar peak amplitudes at ZT2 and ZT15, but different temporal profiles: I_{NaL} has a longer duration at ZT2 than ZT15, and I_{K1} peaks later at ZT2 than ZT15. The changes in these 6 currents lead to an altered I_{Net} waveform and ultimately a lower qNet at ZT2 than ZT15.

We then compared the voltage and current traces for ranolazine at ZT2 and the high-risk drug sotalol at ZT15 (Figure 4). At ZT15, sotalol has a shorter APD

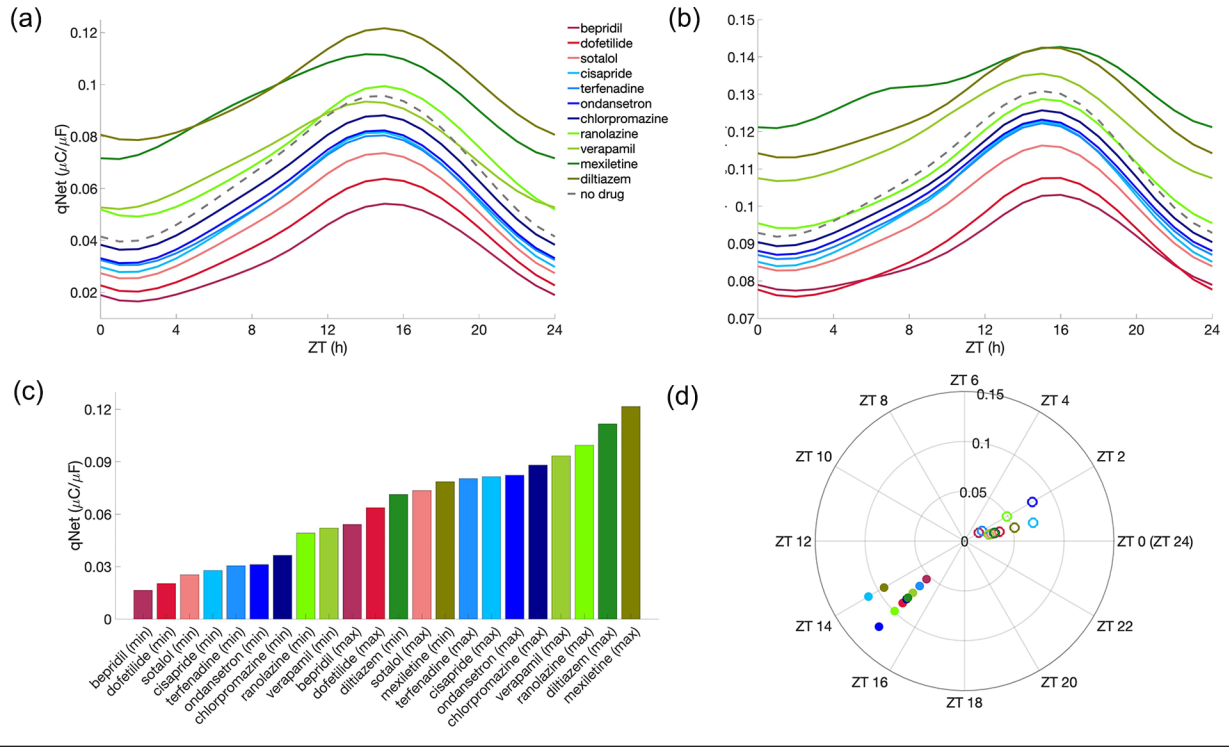

Figure 2. Simulated TdP risk for 11 antiarrhythmic drugs administered at different times of the day. (a) Endocardial qNet values for each drug when administered at each hour (ZT0-ZT24) of the day/night cycle. A lower qNet value indicates higher TdP risk. Drugs previously classified by CiPA as low, medium, and high TdP risk without considering circadian variation are colored various shades of green, blue, and red, respectively. Black curve indicates qNet values when no drug is administered. (b) Same as panel (a), but for epicardial cells. (c) Bar plot showing the endocardial qNet values at the least optimal ZT dosing time (lowest qNet values, bars labeled "min") and the most optimal ZT dosing time (highest qNet values, bars labeled "max") for each drug. (d) Polar plot showing the endocardial max/min qNet values (as radial distance) and most/least optimal dosing times (as polar angle) for each drug. Max qNet values and most optimal dosing times are shown as filled circles, whereas min qNet values and least optimal dosing times are shown as open circles.

than ranolazine at ZT2, and the I_{Net} profile leads to a larger qNet, implying that the classification of TdP risk should be done in a time-of-day–dependent manner.

Finally, we computed a relative qNet score for each drug at each dosing time of day by subtracting the value of qNet with no drug administered from their qNet scores (Figure 5a). The 4 medium-risk drugs had the lowest circadian variation in their relative qNet scores (Figure 5b). For all 3 high-risk drugs, the relative qNet profiles suggest that dosing at ZT13 is optimal for reducing drug-induced TdP risk (Figure 5c). Furthermore, administering these drugs at ZT0 (or equivalently, ZT24) should be avoided as drug-induced TdP risk was highest at that time of day.

DISCUSSION

In this paper, we used computational modeling to explore how circadian rhythms in cardiac electrophysiology affect the safety of antiarrhythmic drugs, with a specific focus on 11 drugs evaluated under the CiPA initiative. Based on our results, we call for circadian physiology and dosing time of day to be incorporated into the CiPA framework in order to more accurately assess proarrhythmia risk across the day/night cycle.

Our study focused on the regulation of ionic conductances by local circadian clocks in cardiomyocytes. Other physical factors that cycle with a 24-h rhythm, such as core body temperature and extracellular ionic conditions, may also influence the TdP risk associated with different times of daily drug administration. Circadian oscillations in these factors can readily be incorporated into the conductance-based modeling formalism underlying the ORd model. The effect of body temperature can be simulated by introducing a temperature scaling factor (Q_{10}) into the ion channel gating variable kinetic parameters (Georgiev et al., 2014; Jabbari and Karamati, 2022). Variations in extracellular ion concentrations can be modeled as changes in ion channel reversal potentials and calculated using the Nernst equation (Barreto and Cressman, 2011; Hübel and Dahlem, 2014).

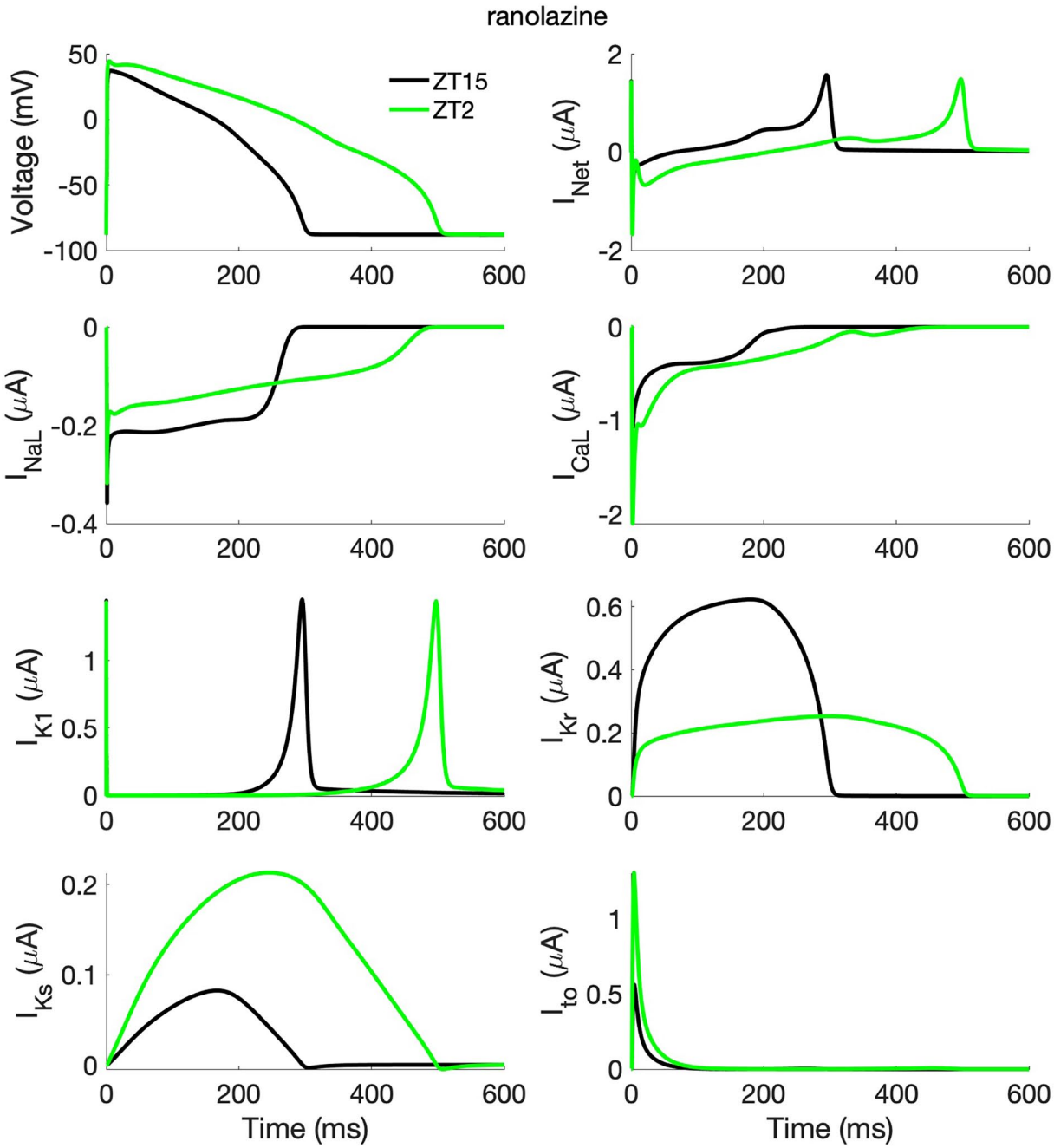

Figure 3. Membrane potential and ionic current traces during an action potential for the low-risk drug ranolazine administered at ZT15 (black) and ZT2 (green).

In addition to local circadian rhythmicity within the heart, the central circadian clock in the suprachiasmatic nucleus also regulates cardiac electrophysiology through the autonomic nervous system. For example, a morning surge in sympathetic drive has been associated with circadian rhythms in ventricular tachycardia, ventricular fibrillation, and sudden cardiac death, possibly due to β-adrenergic stimulation promoting Ca^{2+} overload, delayed afterdepolarizations, and reentry (Black et al., 2019; Gardner et al., 2016). Our model does not include adrenergic signaling, nor other neurohumoral factors, that are potentially important for TdP risk. In a white paper on the general principles underlying CiPA, Li et al. (2020) acknowledge that any *in silico* model can only include a finite number of proarrhythmia mechanisms. The CiPA framework aims to capture the "missing" effects through its other components, such as in vitro experiments with stem cell–derived cardiomyocytes or human electrocardiography (Li et al., 2020; Strauss et al., 2019).

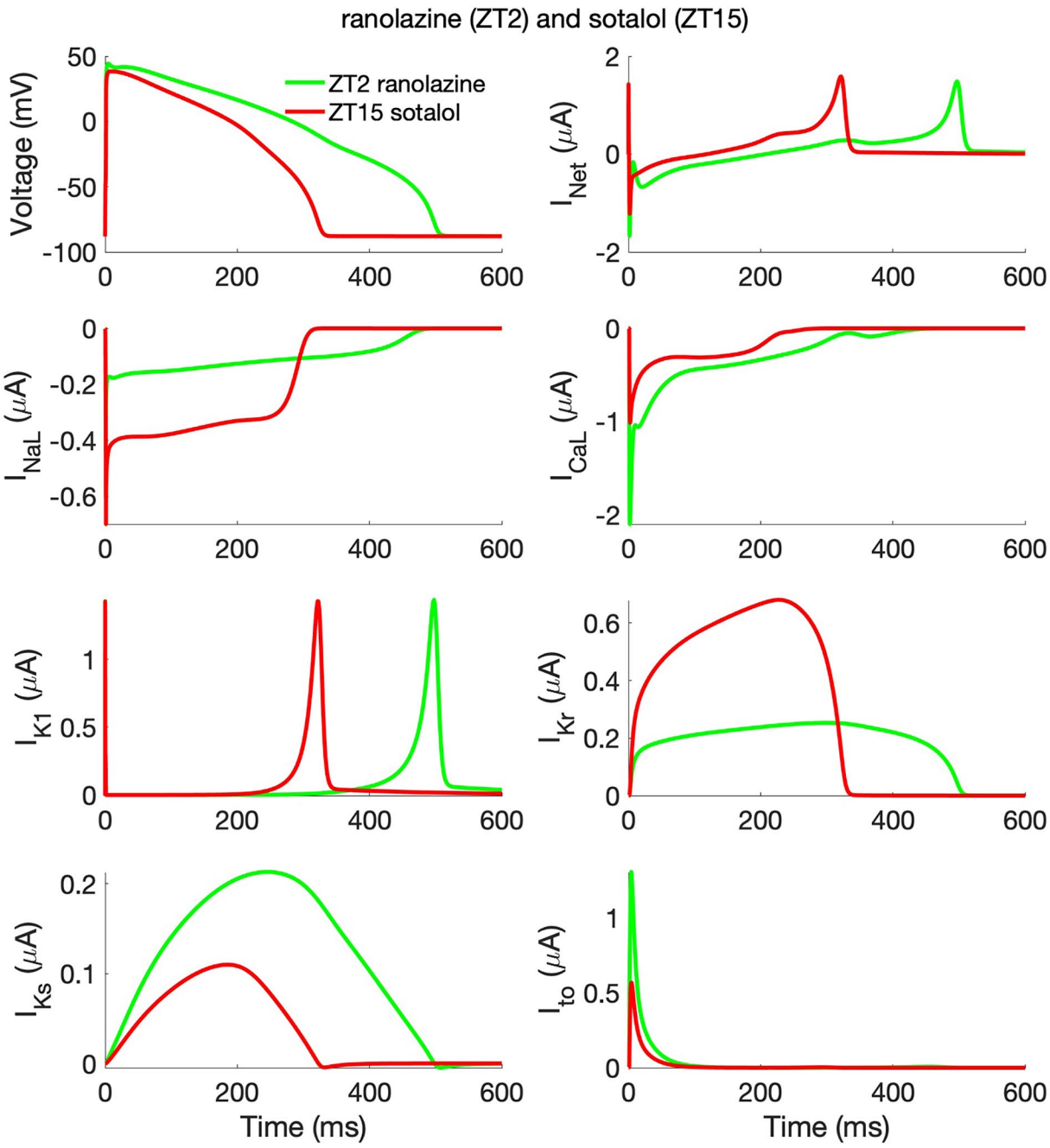

Figure 4. Membrane potential and ionic current traces during an action potential for the low-risk drug ranolazine administered at ZT12 (green) and the high-risk drug sotalol administered at ZT15 (red).

Our approach can readily be extended beyond drug-induced ventricular arrhythmias to evaluate optimal dosing time of day to minimize drug-induced bradyarrhythmias (Devamsh et al., 2023; Tisdale et al., 2020) or drug-induced atrial fibrillation (AF; Kaakeh et al., 2012; van der Hooft et al., 2004). Bradyarrhythmias are indicative of sinus node dysfunction and occur more commonly at night (Black et al., 2019). Li and Kim (2024) recently developed a mathematical model of the regulation of circadian rhythms in heart rate by the autonomic nervous system, circadian rhythms of body temperature, and local circadian rhythmicity in sinoatrial nodal cells that could be used to investigate drug-induced sinus arrhythmias. Paroxysmal AF, defined as AF terminating spontaneously within 7 days, is also more prevalent at night (Black et al., 2019). Although the mechanistic basis of day/night rhythms in AF is not well understood, it has been

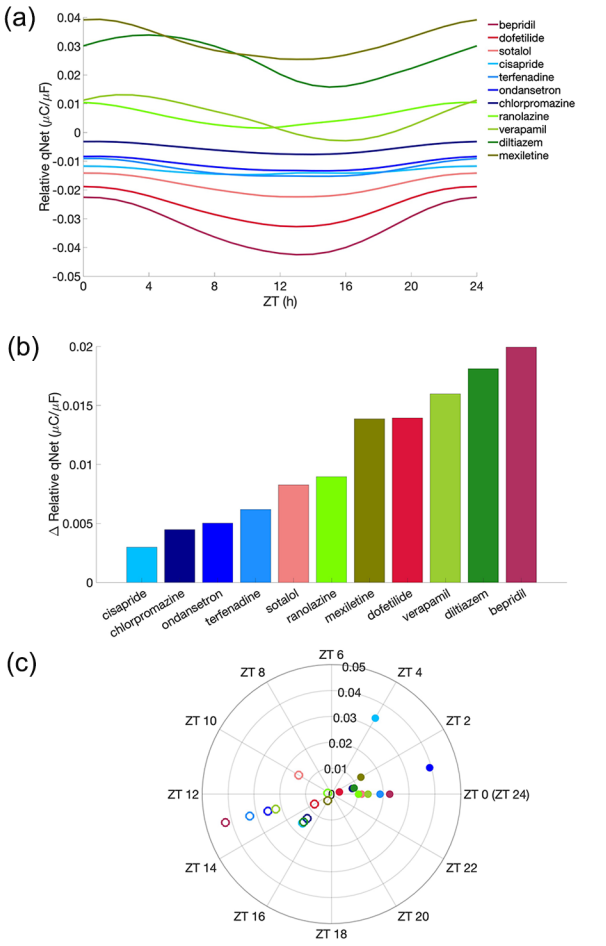

Figure 5. Simulated relative TdP risk for 11 antiarrhythmic drugs administered at different times of the day. (a) Relative qNet values for each drug when administered at each hour (ZT0-ZT24) of the day/night cycle. A negative (positive) relative qNet value indicates the drug increases (decreases) TdP risk. (b) Bar plot showing the amplitude of the change in relative qNet values between the most (highest relative qNet value) and least (lowest relative qNet value) optimal relative ZT dosing time for each drug. (c) Polar plot showing the relative qNet values (as radius) and most/least optimal relative dosing times (as ZT phase) for each drug. Most optimal relative dosing times are shown as filled circles, whereas least optimal relative dosing times as open circles.

shown that 4 potassium channel subunits in mouse atrium exhibit circadian rhythms in expression (Tong et al., 2013). The effects that circadian ion channel remodeling and dosing time have on drug-induced AF could be studied using mathematical models of human atrial APs (Grandi et al., 2011; Heijman et al., 2021). Two of the CiPA drugs we considered here in the context of ventricular arrhythmias (verapamil and diltiazem) have also been reported to potentially induce AF by changing atrial electrical properties (van der Hooft et al., 2004).

Several drug classes that target organ systems other than the heart can still provoke adverse cardiac events (Ruben et al., 2018). It is clear that the circadian clock influences many aspects of cardiovascular function (Diekman and Wei, 2021; Fotiadis and Forger, 2013; Li and Kim, 2024; Young, 2023). Since cardiotoxicity is the leading cause of drug discontinuation, cardiac-related chronopharmacology has potential to improve outcomes across a range of diseases (Ruben et al., 2019).

A limitation of this study is our lack of knowledge on the phase and amplitude of circadian rhythms in cardiac ion channel conductances in human cardiomyocytes. Thus, our simulations of these rhythms are based on animal data. In addition, the masking effects of light and other exogenous factors complicate the translation of experiments performed on endogenous circadian rhythms in constant darkness to light/dark conditions (Gander et al., 1986; Lamont and Amir, 2009). Our results should be regarded as a proof of concept that dosing time of day can impact drug-induced TdP risk, rather than clinical recommendations on the optimal time of day for drug administration.

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CONFLICT OF INTEREST STATEMENT

The authors have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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