

Short-term effects of oral dronedarone administration on cardiac function, blood pressure and electrocardiogram in conscious telemetry dogs

Nakkawee SAENGLUB¹, Brad YOUNGBLOOD³, Carlos DEL RIO³, Suwanakiet SAWANGKOON², Robert L. HAMLIN³ and Anusak KIJTAWORN^{2,4}*

¹Graduate Student in the Program of Animal Physiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand

²Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok 10330, Thailand

³QTest Labs, LLC, 6456 Fiesta Dr., Columbus, Ohio 43235, U.S.A.

⁴Research clusters: Research Study and Testing of Drug's Effect Related to Cardiovascular System in Laboratory Animals, Chulalongkorn University, Bangkok 10330, Thailand

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ABSTRACT. Dronedarone is a multichannel blocking antiarrhythmic drug that has been used for management of atrial fibrillation in humans, but the data in veterinary medicine are inadequate. The objective of this study was to determine the short-term effects of oral dronedarone on cardiac inotropy and lusitropy, blood pressure and electrocardiogram (ECG) in healthy dogs. A total of 6 beagle dogs were instrumented with telemetry units and sono-micrometry crystals to obtain left ventricular pressure-volume relationship, mean blood pressure (MBP) and ECG. Dogs were given orally dronedarone (20 mg/kg, twice per day) for 7 days. All parameters were obtained hourly at 4–8 hr after the first dose and at 12-, 96- (day 4) and 168-hr (day 7) after dosing. The results showed that dronedarone had no effect on inotropy and lusitropy, while it significantly lengthened PQ interval ($P<0.001$) and lowered MBP ($P<0.05$). Dronedarone also tended to reduce cardiac output ($P=0.237$) and heart rate ($P=0.057$). These results suggested that short-term effects of oral dronedarone administration at a dose of 20 mg/kg, twice per day, produced negative dromotropy with minimal effect on cardiac function in conscious dogs.

KEY WORDS: blood pressure, dog, dronedarone, inotropy, lusitropy

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Dronedarone, a class III antiarrhythmic drug, is widely used for treatment of atrial fibrillation (AF) and ventricular arrhythmias in humans [18, 20]. The common oral dose of dronedarone in human medicine is 400 mg, twice per day. After given for 7–14 days, the steady state plasma concentration is 84–167 ng/ml [16]. That dose has produced highly significant changes in heart rate (HR), QT and corrected QT (QTc) intervals and be able to reduce ventricular response rates as well as maintain sinus rhythm in patients with AF [21, 22]. The most common side effects reported in humans are diarrhea, nausea and abdominal pain [16].

The pharmacokinetics of dronedarone in dogs have been studied previously [17]. After single intravenous injection, the plasma dronedarone clearance was 1.8–2.4 l/hr/kg [1]. After oral dosing, the absorption rate in dog was 64–95%, and oral bioavailability in dog was 14–22% [17]. The plasma protein binding in dog was more than 99.5% [17]. Dronedarone was extensively metabolized in dog to form SR35021 and SR90154, and excreted primarily via feces.

As far as we are aware, there is no clinical dose of dronedarone in veterinary medicine. Previous studies have

reported the chronic use of dronedarone in complete atrio-ventricular (CAVB) dogs and conscious telemetry dogs [29, 30]. In CAVB dogs, sustained administration of dronedarone (20 mg/kg, twice per day, orally for 3 weeks) led to lengthening of the QTc interval [30]. On the other hands, chronic dronedarone administration (25 mg/kg, twice per day, orally for 4 weeks) in conscious, normal dogs did not prolong the QTc interval [29]. Both of those studies focused on electrophysiological properties of dronedarone, but their effects on hemodynamic and cardiac function had not been reported.

A dog telemetry model has been validated for sensitivity and specificity recently and used extensively for monitoring electrocardiogram (ECG), blood pressure (BP) and left ventricular pressure simultaneously [2]. The telemetry system allows continuously recording of parameters in conscious animals with free movement, less stress from handling and restraint. The system also provides reliable data without anesthesia artifacts.

Based on successful multicenter clinical trials for management of AF in humans, dronedarone may be beneficial to use in dogs with AF. However, some information (i.e. cardiac function) has not been investigated in conscious dogs. The main objective of this study was to evaluate the left ventricular (LV) function, blood pressure and ECG of repeated oral dose of dronedarone in conscious dogs instrumented with telemetry units to measure LV pressure and volume, BP and ECG. Dogs were also instrumented with sono-micrometry crystals and a vascular occluder to obtain pressure-volume loop relationship for assessment of LV mechanics.

*CORRESPONDENCE TO: KIJTAWORN, A., Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, Henri-Dunant Rd, Pathumwan, Bangkok 10330, Thailand.
e-mail: kanusak@hotmail.com

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MATERIALS AND METHODS

Approvals: This study was approved by the Institutional Animal Care and Use Committee of QTest Labs, LLC, Columbus, OH, U.S.A. (SPD13-012 and SPD13-018). All experimental animal procedures were performed in compliance with QTest IACUC regulation and followed the guidelines outlined in the *Guide for the Care and Use of Laboratory Animals* [15].

Animals: Six healthy mature Beagles of either gender were purchased from Marshall BioResources (North Rose, NY, U.S.A.). They were housed individually from the time of arrival to the end of study in a dog run maintained at a temperature of $21 \pm 2^\circ\text{C}$, a relative humidity of $50 \pm 20\%$ and a 12 hr:12 hr light:dark cycle. All animals were received commercial chow twice daily, and water was provided *ad libitum* in stainless steel containers. Physical examination, routine lead II ECG recording, complete blood count and blood chemistry analysis were performed to evaluate health status in all dogs before beginning of the experiment. Surgical procedures were performed after at least 6 hr period of fasting.

Surgical procedures for telemetry instrumentation: All dogs were given butorphanol (0.1 mg/kg, intravenously) 10 min before receiving propofol (4–6 mg/kg, intravenously, Abbott Laboratories, North Chicago, IL, U.S.A., to effect). Orotracheal intubation was performed and ventilated mechanically with the ascending-bellows, volume-cycled, pressure-regulated ventilator. The ventilator was set to deliver a tidal volume of 12–15 ml/kg (maximum allowed pressure, 20 cmH₂O) at a rate of 8 to 12 breaths per min, sustaining the end-tidal partial pressure of CO₂ between 35 and 45 mmHg and that of O₂ greater than 80 mmHg. The endotracheal tube was connected to a circle anesthetic rebreathing circuit, and anesthesia was maintained with isoflurane in oxygen delivered by a use of vaporizer. The end-tidal inhalant concentration of isoflurane was maintained between 1.4–1.6%. Body temperature was maintained at 36.5–37°C by a warm water heating pump blanket. Each animal was shaved and scrubbed at the surgical areas.

In order to determine oral dose, two dogs were surgically implanted with radiotelemetry transmitters (TL11M2-D70-PCT, Data Sciences International, St. Paul, MN, U.S.A.), which have systemic arterial blood pressure, heart rate, ECG and body temperature data collection capabilities. The procedure for implantation has been described previously [24]. In brief, an incision was made on midline of lower abdomen, and abdominal cavity was exposed. The body of transmitter was sutured on the left abdominal wall to hold the transmitter body. Another incision was made along the left medial thigh, and the femoral artery was exposed by blunt dissection. A blood pressure catheter was passed through the trocar tunneling from abdominal cavity to inguinal area. The femoral artery was ligated distally and incised to insert a blood pressure catheter. The catheter was advanced until the tip resided in the abdominal aorta. Then, the catheter was secured by ligation with 3/0 prolene. The two ECG cables (positive and negative) were positioned by using trocar to tunnel each lead

to the appropriated region to form transthoracic ECG lead (positive: under the left side of the last thoracic cage; and negative: the base of the right side of the neck). The silastic insulator was removed from each lead, and the exposed wire was coiled into a tight loop. The loop of wire was placed and secured in the muscle using a non-absorbable suture material. All incisions were closed using absorbable sutures and sterile staples on the skin. Butorphanol (0.05–0.4 mg/kg, once a day, subcutaneously; Abbott Laboratories), acepromazine (0.05–0.2 mg/kg, once a day, subcutaneously; Butler Animal Health Supply, Dublin, OH, U.S.A.) and cephazolin (15 mg/kg, once a day, subcutaneously; Butler Animal Health Supply) were administered for 7 days. All dogs were allowed to recover for 2 weeks, and transmitter signals were verified before the beginning of the study.

To determine short-term effects of dronedarone on ECG, BP and LV mechanics, four dogs were implanted with radiotelemetry, sono-micrometry crystals, a solid-state pressure transducer, venous occluder and fluid-filled pressure catheters. A left-thoracotomy was performed, and the animal was chronically instrumented with a radio telemetry unit (TL11M3-D70-PCTP, Data Sciences International). The body of transmitter was sutured on the left chest wall behind the scapula. The first pressure catheter was placed into the descending aorta to obtain systemic arterial pressure, while the second pressure catheter was placed into the left ventricular chamber via left apex to obtain left ventricular pressure (LVP). The sono-micrometry crystals (Sonometrics, London, ON, Canada) providing left-ventricular (LV) dimensions/volume were implanted inside the LV muscle at lateral and posterior LV free walls. Additionally, a solid-state pressure transducer (Konigsberg P22, Konigsberg Instruments Inc., Pasadena, CA, U.S.A.) was placed into the LV chamber for pressure monitoring. A hydraulic occluder (OC2, In Vivo Metric, Healdsburg, CA, U.S.A.) was placed/secured around the caudal vena cava, in order to allow its controlled constriction for the generation of LV pressure-volume curves during heterometric auto-regulation. All catheters/wires were aseptically tunneled and externalized between the left and right scapulae. The two ECG electrodes were tunneled subcutaneously and secured to the superficial muscles of the chest wall (modified lead II configuration). Prior to closure, a chest tube was placed for drainage of any fluid and/or gas that accumulates from the surgical procedure. The tube was aspirated twice daily until the amount of fluid removed is less than 35 ml per aspiration in an approximate 24 hr period. Prophylactic antibiotic, pain medication and post-operative care were performed as described previously. If necessary, an additional analgesic may also be administered which may include a fentanyl patch (25–50 µg/hr). All surgical incisions were closed in layers; the underlying musculature was closed with absorbable sutures, and the skin was closed with staples. Throughout the recovery phase, the animals were observed daily for routine signs of recovery, and the wound sites were observed for any signs of potential infections. Animals experiencing pain, distress and/or infections were brought to the attention of the attending veterinarian. The skin incision staples were removed at 7 days after surgery.

All dogs were allowed to recover for 2 weeks, and transmitter signals were verified before the beginning of the study.

Experimental procedures and drug administration: To determine oral dose of dronedarone, two dogs instrumented with TL11M2-D70-PCT were used. Dogs were randomized to receive single oral dose of either placebo or dronedarone (10, 20 or 40 mg/kg). The range of oral dose was chosen based on our preliminary experiment in anesthetized dogs and previous publication in dogs [5, 19, 30]. ECG, BP and temperature were recorded 1 hr before dosing and continued to monitor up to 36 hr after dosing. Since the QT interval is longer during nighttime than during daytime and the QT prolonging drugs have been shown to be more prolonged during nighttime [31], the drug administration was performed at 6 pm in order to clearly observe the effects of drug on QT interval. Due to its short elimination half-life, the washout period between each treatment was at least 14 days, which yield approximately 11–24 times of the half-life [14].

To determine short-term effects of dronedarone on ECG, BP and LV mechanics, the rest of the dogs ($n=4$) were used. Based on the results of single oral dose of dronedarone in our study, each dog was randomized to receive either placebo or dronedarone at a dose of 20 mg/kg, twice per day, for 7 days. The washout period between each treatment was at least 14 days. ECG, BP, LVP and temperature were recorded 1 hr before dosing and continued to monitor up to 7 days after dosing. All parameters including pressure-volume loops were obtained hourly at 4–8 hr after the first dose and at 12-, 96- (day 4) and 168-hr (day 7) after dosing. The detail of generating of pressure-volume loops was previously described [12]. Briefly, at a given time point after dosing, left ventricular preload was acutely reduced by means of brief (approximately 8–10 beats) caudal vena cava occlusions in order to generate a family of pressure-volume curves; approximately three occlusions were performed at each time point, allowing for hemodynamic recovery between occlusions.

Data analysis: Telemetric device was programmed using the Dataquest ART 3.1 software to record electrocardiograms, blood pressure and body temperature. Standard ECG intervals (RR, PQ, QRS and QT) were manually measured by using ECG auto software (EMKA Technologies, Falls Church, VA, U.S.A.). A mean of the averaged 60 sec per timepoint was reported. The QT interval was corrected for heart rate by using van de Water formula (QTc (V)) [27].

Statistical analyses were performed with commercially available software. Data are presented as mean \pm standard error of the mean. Comparisons were made for each parameter in each time point versus the baseline. Differences among time points were determined using one-way ANOVA with repeated measures design. When indicated by a significant F-statistic, specific means were compared by Dunnett's test for multiple comparisons with the baseline. Statistical significance was considered at $P<0.05$ for all analyses.

RESULTS

Effects of a single oral dose of dronedarone on heart rate, ECG parameters and blood pressure: In the first set

of experiment, two dogs were randomly received 3 doses of dronedarone (10, 20 or 40 mg/kg, orally) and placebo. At baseline, the averaged heart rate of both dogs was 86.88 ± 5.59 bpm, and the mean blood pressure was 93.84 ± 8.0 mmHg. The means of PQ, QRS, QT and QTc were 91.15 ± 3.23 ms, 35.44 ± 1.46 ms, 201.9 ± 5.68 ms and 228.54 ± 1.8 ms, respectively. All of single oral doses of dronedarone had no effect on those parameters throughout the monitoring period (36 hr), except for the PQ interval when compared with placebo (Fig. 1A–F). Single oral dose of dronedarone at 40 mg/kg seems to increase the PQ interval clearly from effects of other doses. It can be noticed that heart rate, QRS complex and mean blood pressure were highly variable during the monitoring period.

Effects of repeated oral dronedarone on cardiac contractility: In this study, cardiac contractility was assessed by end-systolic pressure-volume relationship (ESPVR), preload recruitable stroke work (PRSW), contractility index (CI) and dp/dt_{max} (Figs. 2 and 3). Figure 2 shows a family of pressure-volume loops generated after a brief period of posterior vena cava occlusion. Notice that the slopes of those loops were similar when measured at baseline (A), 4 hr after the first dose (B), day 4 (C) and day 7 (D). Overall, the indices of cardiac contractility did not change significantly after short-term dronedarone treatment for 7 days (20 mg/kg, twice per day, orally) when compared with baseline. It could be noticed that at 4 hr after the first dose, the PRSW, CI and dp/dt_{max} were decreased when compared with baseline (15.01%, 10.30% and 12.81%, respectively), but those values did not reach the statistical significance. PRSW and dp/dt_{max} seem to be constant after 12 hr of the first dose until day 7, except for the CI which seems to be increased (13.11%, $P=0.063$) at day 7.

Effects of repeated oral dronedarone on cardiac relaxation: Cardiac relaxation was evaluated by end-diastolic pressure-volume relationship (EDPVR), tau and dp/dt_{min} (Fig. 4A–C). All of relaxation indices measured in this study were highly variable and did not change significantly when compared with baseline. Similar with the inotropic indices, EDPVR and tau seem to be constant at 12 hr after the first dose until day 7.

Effects of repeated oral dronedarone on cardiac output and blood pressure: Short-term administration of dronedarone tended to decrease cardiac output (Fig. 5A) beginning at 4 hr after the first dose (-22.58% , $P=0.273$) until the last timepoint of measurement (day 7, -33.83% , $P=0.273$); however, these decreases did not achieve statistical significance when compared with baseline. The end-systolic volume, end-diastolic volume and stroke volume were unaltered (Fig. 5B). Figure 5C illustrates the systolic (SBP), diastolic (DBP) and mean blood pressures (MBP) in response to short-term dronedarone administration. SBP, DBP and MBP seem to be unaltered from the beginning to 8 hr after the first dose. After 8 hr, all blood pressures started to decline to the level lower than baseline. At days 4 and 7, the decreases of MBP and DBP became constant, and those values were significantly lower when compared with baseline (day 4, -18.23% , $P<0.026$ for MBP; -20.18% , $P<0.018$ for DBP;

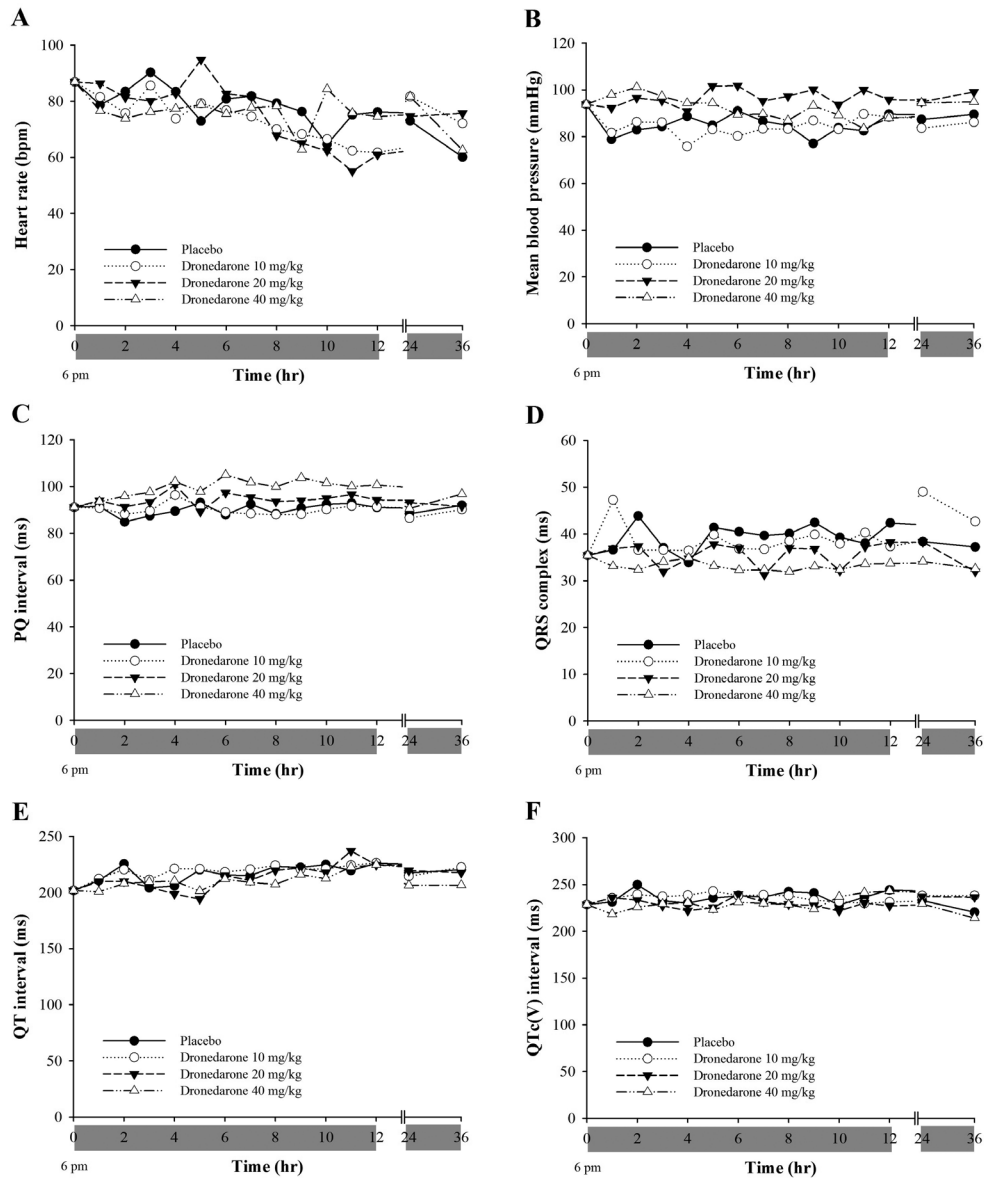


Fig. 1. Effects of single oral dose of placebo or dronedarone (10, 20 and 40 mg/kg) on heart rate (A), mean blood pressure (B), PQ interval (C), QRS complex (D), QT interval (E) and QTc (V) (F) in two conscious dogs instrumented with telemetered unit for obtaining electrocardiograms and blood pressure. Values were obtained from an average of two dogs acquired at baseline, hourly at 1–12 hr, 24 and 36 hr after dosing. Data of each time-pointed were averaged from 1 min. The grey bar on x-axis indicates light-off.

and day 7, -17.76% , $P < 0.044$ for DBP). The LV systolic (LVSP) and LV diastolic pressures (LVDP) were unaltered (Fig. 5D).

Effect of repeated oral dronedarone on heart rate and ECG parameters: In response to short-term dronedarone administration, the heart rate (HR) tended to decrease, and it was almost significant reduction at day 7 (-25.43% , $P = 0.057$) when compared with baseline (Fig. 6A). While QRS complex did not change (data not show), the PQ interval (Fig. 6B) was constant from the beginning until 12 hr after the first

dose. After that, it was significantly lengthened at day 4 and day 7 (21.7% , $P < 0.001$ and 18.01% , $P < 0.001$, respectively). The QT interval (Fig. 6C) was gradually lengthened and almost significantly prolonged at day 4 (9.63% , $P < 0.067$) when compared with baseline. However, when the QT was corrected for heart rate by van de Water formula, it was not significantly prolonged (Fig. 6D).

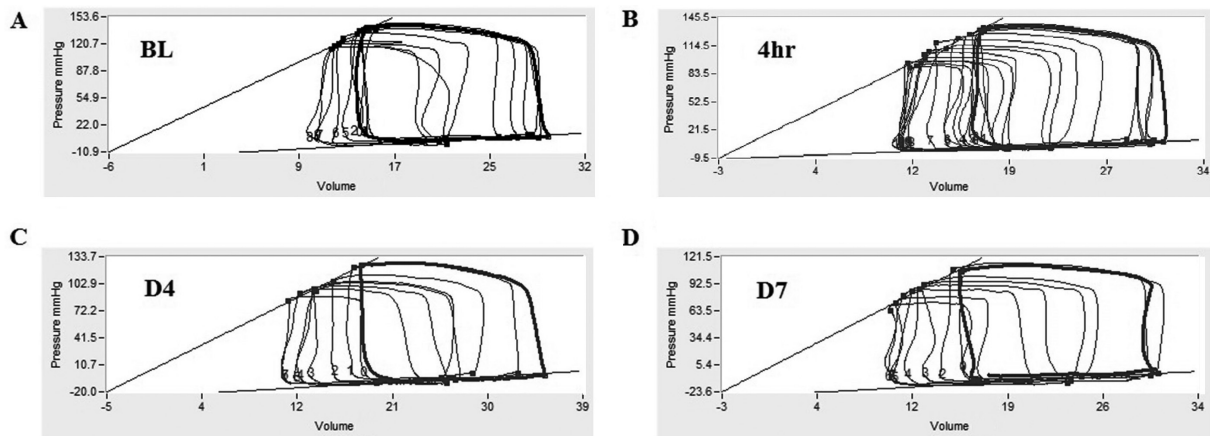


Fig. 2. Representative left ventricular pressure-volume relationship at baseline (A) and after oral dronedarone administration (20 mg/kg, twice per day) at 4 hr after the first dose (B), at day 4 (D4, C) and at day 7 (D7, D) in conscious dogs. The slopes of the end-systolic pressure-volume relationship (ESPVR) were fitted by linear.

DISCUSSION

This study aimed to evaluate the cardiac function, blood pressure and ECG of repeated oral dose of dronedarone (20 mg/kg, twice per day) in conscious dogs instrumented with telemetry units. Although electrocardiographic effects on dronedarone were assessed previously in both anesthetized and conscious dogs [13, 19, 28–30], its inotropic and lusitropic properties had not been evaluated in conscious dogs. Since dogs with atrial fibrillation almost always possess underlying cardiac diseases, drugs for management of AF in veterinary medicine should be given to the patients with caution. Because drugs that alter inotropy and lusitropy might worsen the cardiac function of the patients. We provided the first evidence that short-term dronedarone administration (20 mg/kg, twice per day, orally) for 7 day did not alter cardiac contraction and relaxation, while its electrophysiology is still preserved (i.e. lengthened PQ interval). We have used the pressure-volume loop technique in this study, because it has been accepted as a gold standard to assess the cardiac inotropy and lusitropy [25].

The dose of dronedarone was selected based on our preliminary study and previous publications [5, 19, 28–30]. In literatures, oral doses of dronedarone used in dogs were between 10–30 mg/kg [5, 28–30]. In our previous report, a cumulative dose of intravenous dronedarone at 1.5 mg/kg can prolong PQ interval without adverse effects on cardiac function. In dogs, the absorption is 64–95%, and the oral bioavailability is 14–22% [17]. If a dog, weighing 10 kg, was given oral dronedarone at a dose of 20 mg/kg, the expected dose of dronedarone when given by injection would be between 1.79 to 4.18 mg/kg. Therefore, we decided to vary doses of dronedarone from 10, 20 and 40 mg/kg and administered randomly to our two pilot dogs instrumented with telemetry unit for obtaining ECG and blood pressure. As shown in Fig. 1, we decided to use a dose of 20 mg/kg for the main experiment, since it did not show any dramatically

effect on ECG parameters and did not cause hypotension after an acute dose.

In our main experiment ($n=4$), all dogs were given oral dronedarone for 7 days, and cardiac contractility and relaxation were evaluated. The results showed that dronedarone did not alter the left ventricular inotropy. The slope of PRSW was used as a gold standard, since it is relatively constant among conscious animals [6, 7, 12]. The slope of ESPVR could also be used as a gold standard for measurement of cardiac contractility. However, it has been shown to be curvilinear at higher or lower contractile states [10]. The CI and dP/dt_{max} were also demonstrated consistent with the results of ESPVR and PRSW, even though these two parameters are affected by loading condition [8, 11]. In this study, both active (τ and dP/dt_{min}) and passive (EDPVR) relaxation indices were evaluated, and the results showed that dronedarone did not change neither active nor passive indices of left ventricular relaxation. Similar findings were observed in our previous anesthetized dogs study in which dronedarone had no effect on lusitropy until it was given at a high dose [19]. Therefore, the current study demonstrated that oral dronedarone when given to conscious dogs did not have any significant effects on either inotropy or lusitropy of the left ventricle.

In this study, cardiac output tended to decrease from the beginning of the study and continue to decline until the end of observation time-point. This could be due to heart rate reduction effects of dronedarone, since the stroke volume did not change. It has been demonstrated previously that dronedarone lowers heart rate in both humans and dogs [4, 5, 21, 28–30]. The primary mechanism responsible for the bradycardia effects has been proved to be the inhibition of the funny channel [23]. Mean and diastolic blood pressures were demonstrated to be significantly decreased after short-term dronedarone administration. This is inconsistent with previous data in humans [3, 14]. The hypotension effect of dronedarone may be partly due to a decline in cardiac output

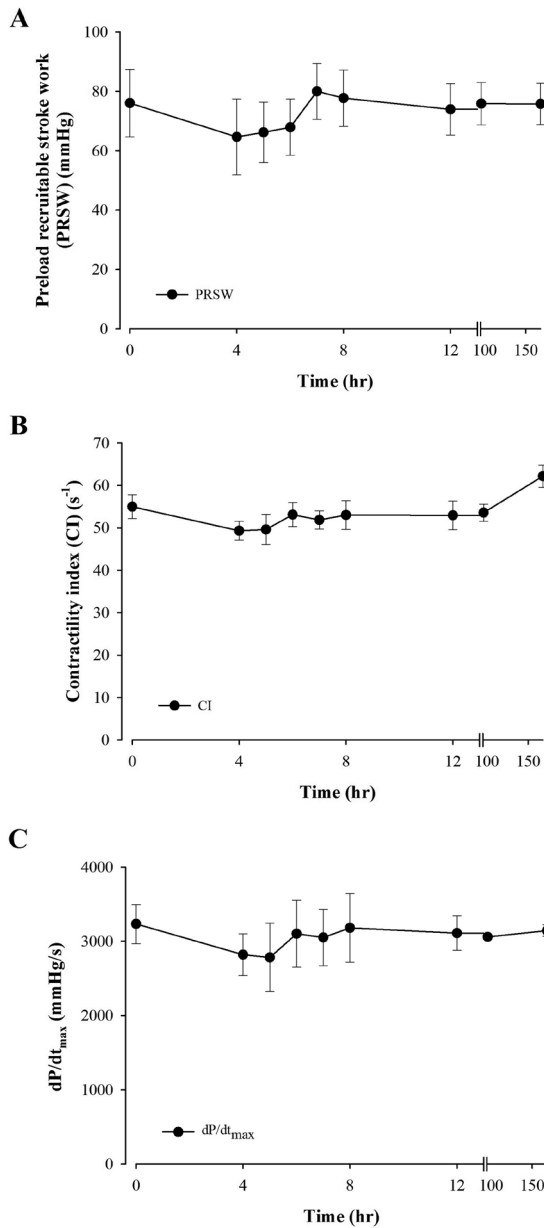


Fig. 3. Effects of oral dronedarone administration (20 mg/kg, twice per day) for 7 days on preload recruitable stroke work (PRSW, A), contractility index (CI, B) and the maximal rate of rise of the left ventricular pressure (dP/dt_{max} , C) in conscious dogs ($n=4$). Values were obtained at baseline (0 hr), 4–8 and 12 hr after the first dose, 96 hr (day 4) and 168 hr (day 7) after dosing.

or mainly due to its α -adrenergic blocking effect [14]. In both conscious and anesthetized dogs, dronedarone at 10 and 30 mg/kg attenuates α -adrenoceptor stimulation demonstrated by a reduction of adrenaline-induced increases in blood pressure [9]. This hypotension effect alerts the veterinary practitioners to be caution when prescribed dronedarone to their patients.

It has been known previously that dronedarone affects

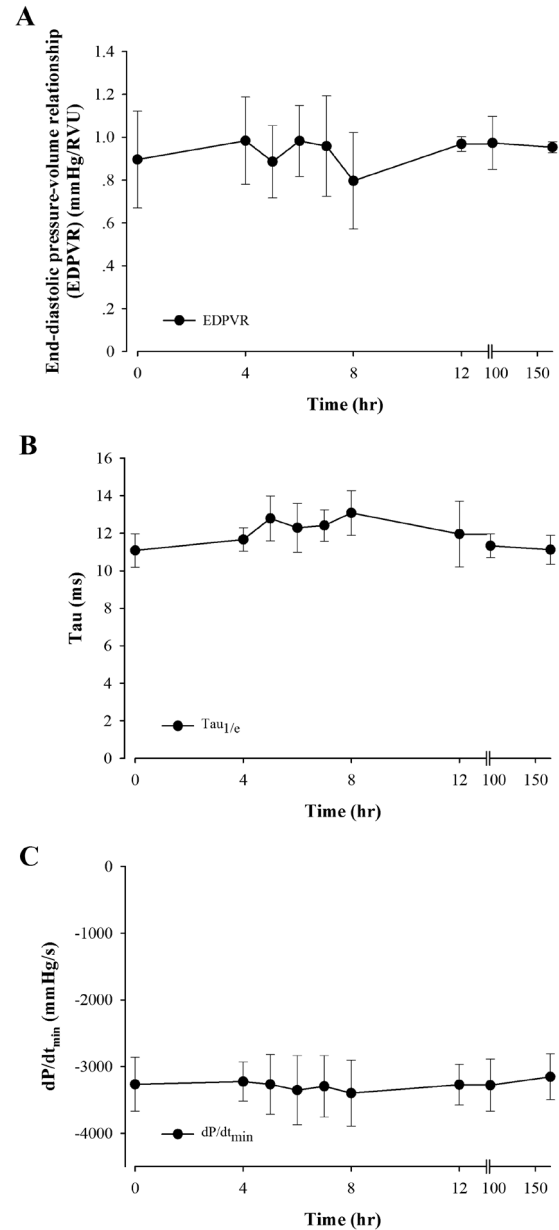


Fig. 4. Effects of oral dronedarone administration (20 mg/kg, twice per day) for 7 days on end-diastolic pressure-volume relationship (EDPVR, A), tau (B) and the maximal rate of fall of the left ventricular pressure (dP/dt_{min} , C) in conscious dogs ($n=4$). Values were obtained at baseline (0 hr), 4–8 and 12 hr after the first dose, 96 hr (day 4) and 168 hr (day 7) after dosing.

PQ interval which may partly be due to decreased firing rate from the sinoatrial node (SAN) or slow conduction velocity from SAN to the head of atrioventricular node [14]. The results of this study confirm the previous findings both in animal experiment and in clinical trials [26, 29]. In this study, the effect of dronedarone on QT and QTc liability confirmed the result of a previous study in conscious normal dogs in which chronic dronedarone administration orally (25

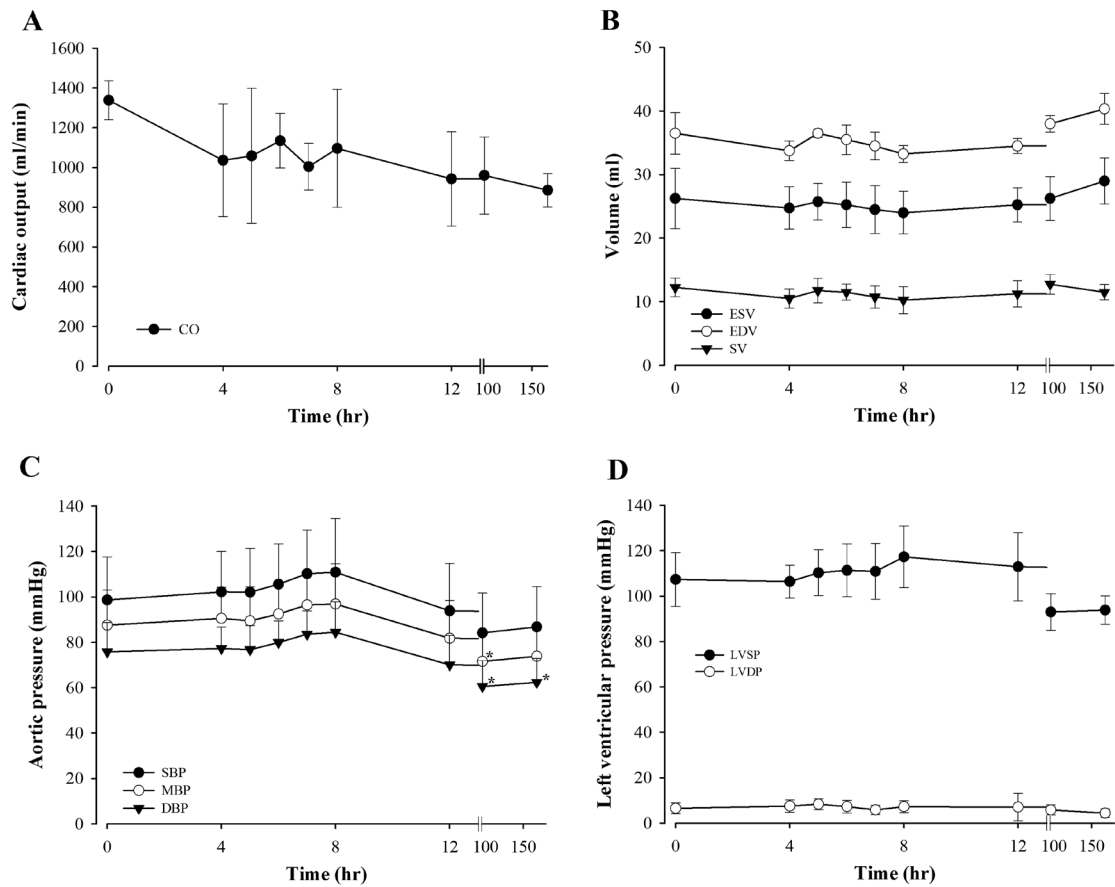


Fig. 5. Effects of oral dronedarone administration (20 mg/kg, twice per day) for 7 days on cardiac output (CO, A), end-systolic volume (ESV), end-diastolic volume (EDV) and stroke volume (B), systolic (SBP), mean (MBP) and diastolic (DBP) blood pressure (C) and left ventricular systolic (LVSP) and diastolic (LVDP) pressures in conscious dogs (n=4). Values were obtained at baseline (0 hr), 4–8 and 12 hr after the first dose, 96 hr (day 4) and 168 hr (day 7) after dosing. *indicates $P < 0.05$.

mg/kg, twice per day, 4 weeks) did not show any effect on QT interval [29]. Our previous data in anesthetized dogs also demonstrated the similar effects on QT and QTc intervals.

The current dog model was instrumented with telemetry units for obtaining ECG, blood pressure and left ventricular pressure together with sono-micrometry crystals and a vascular occluder to obtain pressure-volume loop relationship in conscious state. From our results, the model demonstrates that it is feasible to obtain cardiovascular effects of drugs through the incorporation of contractility and relaxation using sono-micrometry crystal and occlude, while the dog was trained to collect data in the sling. Although the model requires open-chest surgery, all dogs recovered and showed no adverse effects of surgery.

Study limitations: we performed experiment in normal healthy dogs treated with dronedarone (20 mg/kg, twice per day) orally for 7 days. We do not know whether or not this dose is effective for management of AF in dogs. A further study must be investigated the effectiveness of dronedarone (20 mg/kg, twice per day, orally) in AF models in order to assess the effect of dronedarone on cardiac function and

effectiveness of the drug for termination or prevention of recurrence AF. In addition, the plasma drug concentration data should be obtained to see whether the dose levels were correlated with the responses or not.

CONCLUSIONS

We have showed previously that acute administration of dronedarone in anesthetized dogs affects the conduction velocity (lengthened PQ interval) as well as decreases contractility, and worsens lusitropic properties of the left ventricle [19]. In this study, we demonstrated that short-term dronedarone administration (20 mg/kg, twice per day, orally) effectively prolonged PQ interval without any interference with cardiac inotropy and lusitropy, while its effect on PQ interval was still preserved. Therefore, dronedarone possesses minimal potential to worsen the cardiac function in conscious dogs.

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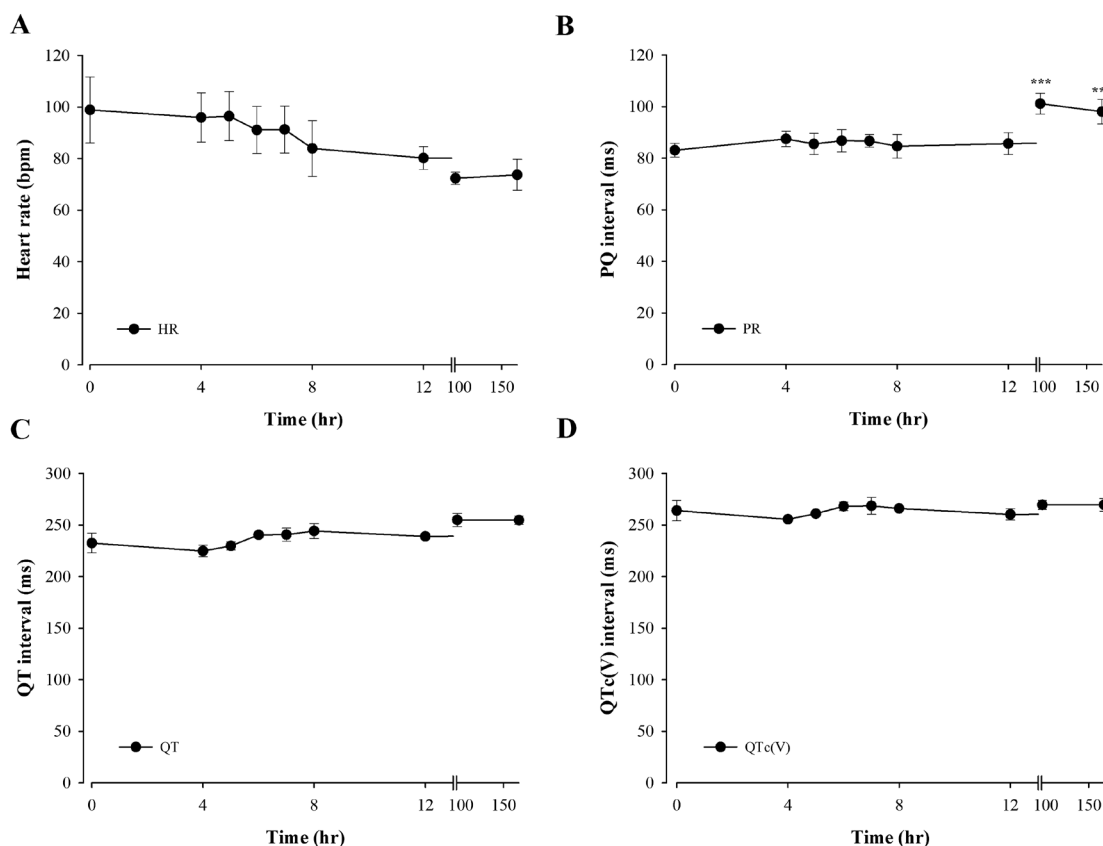


Fig. 6. Effects of oral dronedarone administration (20 mg/kg, twice per day) for 7 days on heart rate (HR, A), PQ interval (B), QT interval (C) and QTc(V) interval (D) in conscious dogs (n=4). Values were obtained at baseline (0 hr), 4–8 and 12 hr after the first dose, 96 hr (day 4) and 168 hr (day 7) after dosing. *** $P < 0.001$.

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