ผลของยาเอมิโอดาโรนและโดรนดาโรนต่อความแปรปรวนของอัตราการเต้นของหัวใจ

การหดตัวของหัวใจ และระดับฮอร์โมนจากต่อมไทรอยด์ในกระต่าย

นางสาววรกาญจน์ บุญเหาะ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Effects of amiodarone and dronedarone on heart rate variability, cardiac contractility, and thyroid hormone levels in rabbits

Miss Worakan Boonhoh

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Animal Physiology
Department of Veterinary Physiology
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Thesis Title	Effects of amiodarone and dronedarone on heart rate variability, cardiac contractility, and thyroid hormone levels in rabbits
By	Miss Worakan Boonhoh
Field of Study	Animal Physiology
Thesis Advisor	Assistant Professor Dr. Suwanakiet Sawangkoon, Ph.D.

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วรกาญจน์ บุญเหาะ : ผลของยาเอมิโอดาโรนและโดรนดาโรนต่อความแปรปรวนของอัตราการเต้นของหัวใจ การหดตัวของหัวใจ และระดับฮอร์โมนจากต่อมไทรอยด์ในกระต่าย (Effects of amiodarone and dronedarone on heart rate variability, cardiac contractility, and thyroid hormone levels in rabbits) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. น.สพ. ดร. สุวรรณเกียรติ สว่างคุณ, หน้า.

ยาเอมิโอดาโรนและยาโดรนดาโรนเป็นยารักษาภาวะหัวใจเต้นผิดจังหวะกลุ่มที่ ๓ มีโครงสร้างทางเคมีที่คล้ายกัน แต่ต่างกันที่ยาเอมิโอดาโรนนั้นมีไอโอดีนเป็นส่วนประกอบอยู่ในโครงสร้างโมเลกุล เนื่องจากข้อมูลการศึกษาของยาทั้งสองในกระต่ายมีอย่างจำกัด ทำให้ผู้วิจัยประสงค์ที่จะศึกษาผลของยาทั้งสองชนิดต่อความแปรปรวนของอัตราการเต้นของหัวใจ การหดตัวของหัวใจ และระดับฮอร์โมนจากต่อมไทรอยด์ ในกระต่ายเพศผู้จำนวน ๑๖ ตัวที่แบ่งเป็นสองกลุ่มการทดลองเพื่อให้ยาเอมิโอดาโรนและยาโดรนดาโรน โดยป้อนยาเข้ากระเพาะอาหารในขนาดยา ๕๐ มก./กก./วัน นาน ๗ วัน แล้วจึงให้ขนาดยา ๑๐๐ มก./กก./วัน ต่ออีก ๗ วัน ในวันสุดท้ายของแต่ละช่วงได้ทำการเก็บข้อมูลคลื่นไฟฟ้าหัวใจของกระต่ายในขณะรู้สึกตัว จากนั้นได้ทำการบันทึกและวิเคราะห์การทำงานของหัวใจด้วยคลื่นเสียงสะท้อนความถี่สูงแบบมาตรฐานและแบบสเป็กเคิลแทร็กกิ้งพร้อมกับเก็บตัวอย่างเลือดจากกระต่ายขณะที่ถูกวางยาสลบ จากการศึกษาพบว่ายาทั้งสองชนิดในขนาดยา ๑๐๐ มก./กก./วัน นั้นทำให้อัตราการเต้นของหัวใจลดลง ความแปรปรวนของอัตราการเต้นของหัวใจชนิดความถี่รวม ความถี่ต่ำ และสัดส่วนของความถี่ต่ำต่อความถี่สูง ต่างลดลงอย่างมีนัยยะสำคัญ การทำงานของหัวใจเมื่อทำการวิเคราะห์คลื่นเสียงสะท้อน-ความถี่สูงแบบมาตรฐานและแบบสเป็กเคิลแทร็กกิ้งในทุกช่วงการทดลองนั้นไม่พบความแตกต่างกันยกเว้นเฉพาะอัตราการเปลี่ยนแปลงของขนาดเส้นรอบวงกล้ามเนื้อหัวใจเทียบกับเวลาลดลงในกลุ่มที่ให้ยาเอมิโอดาโรนในขนาด ๕๐ มก./กก./วัน ระดับของฮอร์โมนไทรอกซินมีการเพิ่มขึ้นอย่างมีนัยสำคัญในกลุ่มที่ให้ยาเอมิโอดาโรนแต่ลดลงในกลุ่มที่ให้ยาโดรนดาโรน จากการทดลองสรุปได้ว่ายาทั้งสองชนิดมีผลทำให้ค่าความแปรปรวนของอัตราการเต้นของหัวใจลดลงใกล้เคียงกันซึ่งอาจเกิดจากการกดการทำงานของระบบซิมพาเทติก และยังพบว่าการวิเคราะห์คลื่นเสียง-สะท้อนความถี่สูงแบบสเป็กเคิลแทร็กกิ้งนั้นให้ข้อมูลได้มากขึ้นแต่ไม่ได้มีความไวต่อการเปลี่ยนแปลงของการทำงานของหัวใจมากไปกว่าแบบมาตรฐานซึ่งยาเอมิโอดาโรนมีแนวโน้มลดการบีบตัวของหัวใจมากกว่ายาโดรนดาโรนในโมเดลนี้ นอกจากนี้ยาทั้งสองชนิดต่างรบกวนการทำงานของต่อมไทรอยด์ โดยที่ยาเอมิโอดาโรนทำให้เกิดภาวะฮอร์โมนไทรอยด์เป็นพิษ ส่วนยาโดรนดาโรนทำให้เกิดภาวะพร่องฮอร์โมนไทรอยด์ในกระต่าย

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5675507231 : MAJOR ANIMAL PHYSIOLOGY
KEYWORDS: AMIODARONE / DRONEDARONE / HEART RATE VARIABILITY / CARDIAC CONTRACTILITY / THYROID HORMONE

WORAKAN BOONHOH: Effects of amiodarone and dronedarone on heart rate variability, cardiac contractility, and thyroid hormone levels in rabbits. ADVISOR: ASST. PROF. DR. SUWANAKIET SAWANGKOON, Ph.D., pp.

Amiodarone (AM) and dronedarone (DR) are class III antiarrhythmic agents that have similar chemical structures, except AM contains iodine molecules. Due to the limited data available in rabbits, the effects of both drugs on heart rate variability (HRV), contractility and thyroid hormone levels were studied. Sixteen male New Zealand white rabbits were used and divided into 2 groups received AM or DR. The rabbits were gavaged either AM or DR at dosages of 50 (AM50, DR50) and 100 mg/kg/day (AM100, DR100) continuously for a period of 7 days each. On the last day of each period, electrocardiograms were recorded from the conscious rabbits, while standard echocardiograms (Echo), speckle tracking echocardiograms (STE) and blood samples were collected from the anesthetized rabbits afterward. The HRV results showed that AM100 and DR100 decreased heart rate, total power, low frequency component, and low to high frequency ratio significantly compared to the baselines. All echocardiographic parameters of both agents in every period were no significant difference from their baselines, except global circumferential plane strain rate at basal segmental level of AM50 that was decreased. Thyroxine levels were significantly increased in AM treatments but decreased in DR treatments of treatment period 1 and 2 compared to their baseline. In conclusion, both AM and DR reduce HRV which may be due to sympathetic suppression. STE may provide more information but not give higher sensitivity than Echo in our study, despite the fact that AM may have more negative inotropic effect than DR in this model. Nevertheless, both drugs produced thyroid dysfunction in the different way, thyrotoxicosis in AM but hypothyroidism in DR.

Department: Veterinary Physiology Student's Signature .....
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CONTENTS

Page

Page

Page

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AF	Atrial fibrillation
AIH	Amiodarone induced hypothyroidism
AIT	Amiodarone induced thyrotoxicosis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM50	The amiodarone treatment period 1 of protocol with amiodarone 50 mg/kg/day for 7 days
AM100	The amiodarone treatment period 2 of protocol with amiodarone 100 mg/kg/day for 7 days
ANS	Autonomic nervous system
APD_{50}	Action potential duration 50%
APD_{90}	Action potential duration 90%
AST	Aspartate aminotransferase
Avg	Average
Beta-MHC	Beta-myosin heavy chain
bpm	Beats per minute
BUN	Blood urea nitrogen
CBC	Complete blood count
CO	Cardiac output
Cr	Creatinine
D_LCO	Capacity of carbonmonoxide diffusion
DEA	Desethylamiodarone
dP/dt max	Maximal first derivation of left ventricular pressure
dP/dt min	Minimal first derivation of left ventricular pressure
DR50	The dronedarone treatment period 1 of protocol with dronedarone 50mg/kg/day for 7 days
DR100	The dronedarone treatment period 2 of protocol with dronedarone 100 mg/kg/day for 7 days

ECG	Electrocardiography
EDV	End-diastolic volume
EDTA	Ethylenediaminetetraacetic acid
EF	Ejection fraction
EMIAT	European myocardial infarct amiodarone trial
ERP	Effective refractory period
ESV	End-systolic volume
ET	Ejection time
FAC	Fractional area change
FDA	The US food and drug administration
FS	Fractional shortening
GCPS	Global circumferential plane strain
GCPSR	Global circumferential plane strain rate
GGT	Gamma-glutamyl transferase
GRPS	Global radial plane strain
GRPSR	Global radial plane strain rate
HF	High frequency
HRV	Heart rate variability
IACUC	The institutional animal care and use committee
$I_{Ca(L)}$	L-type calcium currents
I_{KAch}	Muscarinic acetylcholine receptor-coupled potassium current
I_{Kr}	Rapidly activating delayed-rectifier potassium current
I_{Ks}	Slowly activating delayed-rectifier potassium current
I_{K1}	Inward rectifier potassium current
I_{Na}	Sodium current
I_{sus}	Sustained potassium current
IVCT	Isovolumic contraction time
IVRT	Isovolumic relaxation time

IVSd	Interventricular septum diameter during diastole
IVSs	Interventricular septum diameter during diastole
LVIDd	Left ventricular internal diameter during diastole
LVIDs	Left ventricular internal diameter during systole
LVPWd	Left ventricular posterior wall diameter during diastole
LVPWs	Left ventricular posterior wall diameter during systole
LF	Low frequency
LV	Left ventricle
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentrations
MCV	Mean corpuscular volume
MPV	Mean platelet volume
NCX	Sodium-calcium exchanger
PEP	Pre-ejection period
PSAXAP	Parasternal short axis at apical segmental level
PSAXB	Parasternal short axis at basal segmental level
PSAXM	Parasternal short axis at middle segmental level
RBC	Red blood cells
SEM	Standard error of mean
SERCA	Sarcoplasmic reticulum calcium ATPase
SR	Strain rate
St	Strain
STE	Speckle tracking echocardiography
SV	Stroke volume
TdP	Torsade de pointes
TDI	Tissue doppler imaging
TPSD	Time to peak standard deviation
TP	Total protein

TR	Thyroid hormone receptor
t_{max}	The duration to reach peak plasma
T_3	3,5,3'-triiodothyronine
T_4	Thyroxine
ULF	Ultra-low frequency
VLF	Very low frequency
V_{Max}	Maximum upstroke velocity of the action potential
WBC	White blood cell

CHAPTER I
INTRODUCTION

1.1 Importance and Rationale

Amiodarone and dronedarone are potent multichannel blocking agents, classified as a class III antiarrhythmic drug of the Vaughan Williiam's system, whereas they have potentials to cover all 4 classes of antiarrhythmic drugs (Singh, 2006; Singh et al., 2007). These agents are mostly metabolized by the liver and highly protein-bounding. Both of them have similar chemical structures, which drondarone is a non-iodinated benzofuran derivative of amiodarone. Amiodarone has two iodine molecules which shares some similar structures to thyroxine (Vassallo and Trohman, 2007). Therefore, using amiodarone may alter thyroid hormone level and may interfere thyroid hormone function. It could be either amiodarone-induced thyrotoxicosis (AIT) or amiodarone-induced hypothyroidism (AIH) (Martino et al., 2001). Dronedarone was reported that it might have lower effect or not change on thyroid hormone levels (Chatelain et al., 1995; Pantos et al., 2002), but it may mimic hypothyroidism such as decreasing heart rate and cardiac contractility (Pantos et al., 2005). Many studies have shown that dronedarone selectively blocked either thyroid hormone receptor (TR) $alpha_1$ (Pantos et al., 2005) or TR $bata_1$ in cardiac myocytes, similar to amiodarone (Stoykov et al., 2007). The results of acute and chronic antiarrhythmic effects of amiodarone and dronedarone on ventricles were comparable (Gautier et al., 2003). Moreover, amiodarone and dronedarone might have negative inotropic effect, cause by antiarrhythmic class II and IV actions which block beta-adrenergic receptor and calcium channel, respectively (Kodama et al., 1997; Patel et al., 2009). A previous research has shown that these 2 agents had negative inotropic effect measured by decreasing maximal first derivation of left ventricular pressure (dP/dt max) in isolated ventricular myocytes of Guinea pig hearts (Gautier et al., 2003). However, a study in anesthetized pigs revealed that dronedarone did not change cardiac contractility dP/dt max (Sobrado et al., 2013). Both amiodarone and dronedarone prolonged action potential duration 50% (APD_{50})

and 90% (APD_{90}) as well as QT interval due to their multichannel blocking properties (Sun et al., 2002). Amiodarone and dronedarone treatment may alter sympatovagal balance and cause heart rate variability (HRV) changing due to their beta-adrenergic blocking action. A prospective study found that prophylactic treatment with amiodarone tended to improve HRV and reduced mortality rate in patients with myocardial infarction who had HRV depressing (Malik et al., 2000). Moreover, intravenous amiodarone administration increased HRV in rats. Vagal activity was acutely raised significantly after injection while sympathetic activity was increased shortly and decreased significantly afterward (Dias Da Silva et al., 2002a). In addition, a rabbit model is worldwide useful for study the cardiovascular system that refers to human heart function. The rabbit and human heart share similarity important cardiac compositions, such as beta-myosin heavy chain (bata-MHC), sarcoplasmic reticulum calcium ATPase (SERCA) and sodium-calcium exchanger (NCX) expressions.

There are several invasive or non-invasive techniques to evaluate cardiac functions, for instance cardiac imaging techniques, electrocardiography, blood test, auscultation etc. Transthoracic echocardiography is a non-invasive method of cardiac imaging techniques to assess cardiac functions. It is not only important for diagnosis, prognosis, management, and treatment of heart diseases but also to understand pathophysiology of cardiac diseases. Standard 2D, M-mode, Doppler and Tissue Doppler imaging (TDI) echocardiography are practical standard approach to evaluate left ventricular (LV) function, the largest and most important part of the heart. Speckle tracking technique echocardiography (STE) is the TDI derived technique. It is well-known in strain (St) and strain rate (SR) parameters. STE was introduced for quantitative assessments of myocardium deformation. It has been presumed that St and SR by STE would be more sensitive to detect myocardial dysfunction and assess abnormal regional contraction than standard echocardiography.

In the present study, we would like to compare effects of amiodarone and dronedarone on HRV, cardiac contractility and thyroid hormone levels in rabbits. Moreover, the new developed echocardiographic technique, STE, might need to be

evaluated the potential for assessment of cardiac function compare to standard echocardiography.

1.2 Objectives

1.2.1 To compare effects of amiodarone and dronedarone on HRV, cardiac contractility and thyroid hormone level in rabbits

1.2.2 To study an updated echocardiography technique, STE, on rabbit's cardiac function compares to standard echocardiography

1.3 Hypotheses

1.3.1 Amiodarone and dronedarone affect HRV, cardiac contractility and thyroid hormone levels.

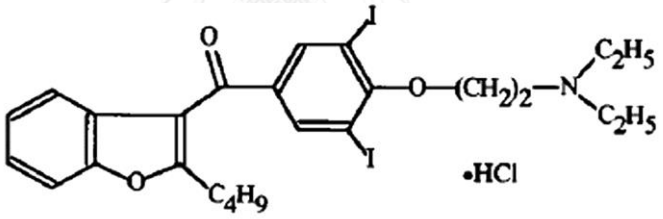
1.3.2 STE provides more sensitive cardiac function parameters than standard echocardiography.

CHAPTER II

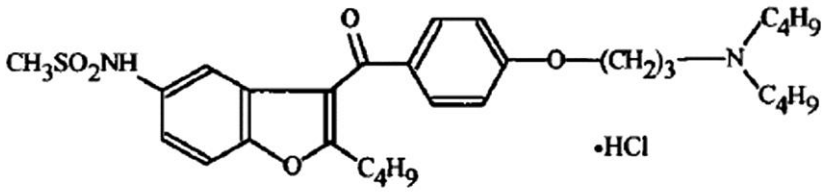
LITERATURE REVIEWS

2.1 Amiodarone and dronedarone

Amiodarone and dronedarone (Figure 1) are complex antiarrhythmic agents with various electrophysiological effects. Amiodarone was discovered more than 40 years. The US Food and Drug Administration (FDA) recommended “amiodarone” for life-threatening ventricular arrhythmia treatment, and it can be used for atrial fibrillation treatment (Singh, 2006). Due to its serious side effects, such as abnormal thyroid hormone levels, hepatotoxicity and pulmonary fibrosis, a new analog “dronedarone” was synthesized by deiodination and modification of chemical structures to reduced side effects of amiodarone. The FDA approved dronedarone in 2009 for atrial fibrillation (AF) or atrial flutter treatment (Sanofi-Aventis, 2009).



Amiodarone (MW=682)



SR33589B/Dronedarone (MW=593)

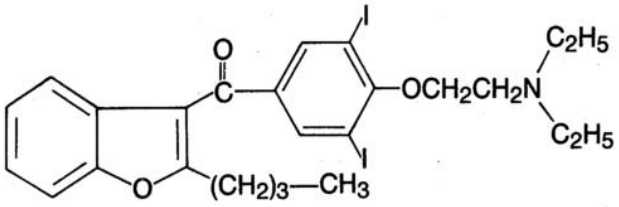
Figure 1 Chemical structures of amiodarone (upper) and dronedarone (lower) (Sun et al., 1999).

2.2 Pharmacokinetic study in human

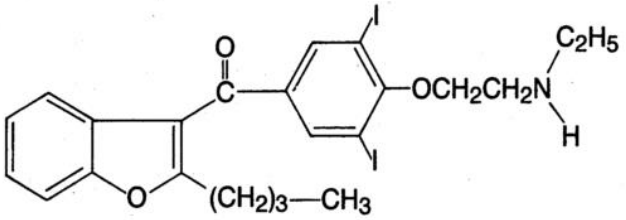
Amiodarone and dronedarone are benzofuran compounds. Amiodarone is highly lipophilicity and slowly absorbed though the gastrointestinal tract. Oral bioavailability of amiodarone is variable, ranging from 20 to 86% in humans (Latini et al., 1984; Zipes et al., 1984; Nattel and Talajic, 1988). The duration to reach the peak plasma concentration (t_{max}) of amiodarone is unpredictable from 2 to 10 hours (Sloskey, 1983; Zipes et al., 1984; Roden, 1993). There is a suggestion for taking amiodarone with food that can increase drug absorption rate (Gill et al., 1992). Amiodarone is highly protein bound approximately more than 98% in humans (Andreasen et al., 1981). Amiodarone and its metabolite, desethylamiodarone (DEA) (Figure 2), tend to accumulate in high lipid content tissues, for example red blood cell membrane, adipose tissue, liver, and heart. Moreover, free DEA is more likely to bind to cardiac tissue more than amiodarone (Roden, 1993). The main elimination routes of amiodarone and DEA are biliary excretion and less than 1% renal excretion (Gill et al., 1992). Therefore, it is safe to use in patients with renal impairment. Amiodarone is metabolized mostly by enzymes CYP3A4 and CYP2C8 in the liver and partially in the small intestine. Since the activity of a CYP3A4 isoenzyme has a large inter-individual variation. Thereby, the oral amiodarone bioavailability has been reported in a wide range (Pfeiffer et al., 1990). The average half-life of amiodarone for single dose either orally or intravenously was reported various from 3.2 to 36 hours (Andreasen et al., 1981; Gill et al., 1992). For long term maintenance doses around 200-600 mg/day PO, amiodarone terminal half-life was 53 days and may be vary between 13 and 107 days and its metabolite half-life was longer, approximately 61 days (Zipes et al., 1984; Gill et al., 1992).

Drondarone is a non-iodinated benzofuran derivative antiarrhythmic agent (Figure 1). It was developed to reduce adverse effects of amiodarone on the thyroid hormone dysfunction problem. The iodine moieties in the original amiodarone were deleted, and a methanesulfonyl group was added to the benzofuran ring of dronedarone, which caused of the lipid-soluble property decreasing and plasma half-life shortening. Taking dronedarone via oral route is barely absorbed when fasting

(Sanofi-Aventis, 2009). Absolute bioavailability of dronedarone orally is approximately 4% but can be increased 2 to 5 folds to 15% when taking with high fat meal. The drug distribution is widely throughout the body such as kidney, liver, spleen, lung and myocardium (Hoy and Keam, 2009; Sanofi-Aventis, 2009). Moreover, dronedarone is metabolized mainly by hepatic enzymes, CYP3A4, and barely by CYP2D6. Its metabolite is N-debutyl metabolite. The metabolite has pharmacokinetic profiles similar to the parent compound. However, antiarrhythmic effect of N-debutyl metabolite is lower than dronedarone (Sanofi-Aventis, 2009). Both dronedarone and its metabolite are highly bound to plasma protein 98%, mostly with albumin. The majority of excreted route is 84% via the bile system and a little, approximately 6 %, via renal excretion, (Patel et al., 2009; Rosa et al., 2014). The plasma elimination half-life of dronedarone in human is between 13 and 19 hours (Sanofi-Aventis, 2009).



Amiodarone



Desethylamiodarone

Figure 2 Chemical structures of amiodarone (upper) and its active metabolite, desethylamiodarone (DEA) (lower) (Gill et al., 1992)

2.3 Anti-arrhythmic actions

Amiodarone and dronedarone are well-known as multichannel blocking agents, because their effects cover all 4 antiarrhythmic classes of the Vaughan Williams system (Singh, 2006; Singh et al., 2007), including class I: sodium channel blockade, class II: adrenergic receptor blockade, class III: potassium channel blockade, and class IV: calcium channel blockade. However, both agents are classified as class III antiarrhythmic drugs. Their electrophysiological properties might have different effects on individual ion channels. In isolated guinea pig ventricular cells, amiodarone and dronedarone inhibit potassium currents, including rapidly activating delayed-rectifier potassium current (I_{Kr}), slowly activating delayed-rectifier potassium current (I_{Ks}), and inward rectifier potassium current (I_{K1}) (Gautier et al., 2003). There were evidences showed that both agents reduced muscarinic acetylcholine receptor-coupled potassium current (I_{KAch}) in isolated rabbit heart cells from sinoatrial node (Altomare et al., 2000) and sustained potassium current (I_{sus}) in isolated rat cardiomyocytes (Kathofer et al., 2005). Moreover they also inhibit sodium (I_{Na}) and L-type calcium ($I_{Ca(L)}$) currents. Therefore, the Maximum upstroke velocity of action potential (V_{max}) was decreased via sodium channel blocking property of the agents (Gautier et al., 2003). The comparison effects of amiodarone and dronedarone had been studied for over decades to identify the superior antiarrhythmic effect. Dronedarone inhibited I_{KAch} by reduced GTP-binding protein of the K_{Ach} channel more effective than amiodarone in isolated atrial cell of guinea pig (Guillemare et al., 2000). In the human isolated atrial myocyte experiment, acute dronedarone administration inhibited I_{Na} significantly more effective than amiodarone at 3 μM (97±4% and 41±11%, respectively). There was a discussion that iodine molecules of amiodarone was not responsible to acute effect on cardiac sodium channels (Lalevee et al., 2003). In 1999, Sun and coworkers demonstrated that chronic oral treatment of amiodarone and dronedarone were comparable on electrophysiology in isolated rabbit papillary muscle and the sinoatrial node; increased APD_{50} and APD_{90} and reduced V_{Max} (Sun et al., 1999). Another research of Sun and coworkers in 2002, studied isolated ventricular myocytes of rabbits with chronic oral dronedarone and

amiodarone treatments for 3 weeks. The results showed significantly prolongation of APD90, effective refractory period (ERP), RR interval, QT interval and QTc interval. In contrast, acute effects of these agents markedly reduced APD90 and ERP. These suggestions were similar potentials against arrhythmias of amiodarone and dronedarone (Sun et al., 2002). The effects of these agents are mostly dose-dependent. However, a study in acetylcholine-induced AF in isolated canine atria indicated that acute amiodarone had significantly higher efficiency to terminate AF than acute dronderone at the concentration of 10 mM by increased APD_{90} and ERP, and decreased V_{Max} (Burashnikov et al., 2010). Additionally, amiodarone and dronedarone effects were mostly similar on adrenergic receptors; inhibition of alpha-adrenoceptor which associated with blood pressure reduction as well as inhibition of bata-adrenoceptor which related to decreased contractility and heart rate. Nevertheless, dronedarone inhibited $beta_2$-adrenoceptor better than amiodarone, while amiodarone markedly flavored to inhibit $bata_1$-adrenoceptor more than dronedarone in anesthetized dogs (Hodeige et al., 1995). Moreover, amiodarone and dronedarone reduced TR $alpha_1$ and $beta_1$ expression in rat right atrial myocytes and also decreased TR $bata_1$ expression in rat left ventricular (LV) myocytes. These inhibition effects resulted in slowly heart rate (Stoykov et al., 2007). In the past, there was a myth about antiarrhythmic effects of amiodarone that may cause by AIH, rather than its direct multichannel blocking effect of amiodarone. Bosch and coworkers revealed these results that chronic amiodarone and hypothyroidism differently acted on ionic currents in guinea pig myocytes, whereas I_{Ks} was markedly decreased in hypothyroidism (Bosch et al., 1999). Amiodarone is widely used for control rhythm of ventricular and supraventricular tachyarrhythmia (Singh, 2006). Intravenous amiodarone injection in pediatrics was safe and the antiarrhythmic effects are similar to oral route (Figa et al., 1994; Masi et al., 2009). Many animal models were studied and shown the results of comparable effects of dronedarone and amiodarone on antiarrhythmic effect. Dronedarone decreased both ventricular tachycardia and fibrillation, and also reduced mortality rate same as amiodarone did in a rat model (Manning et al., 1995). The results were also similar in the anesthetized pig experiment (Finance et al., 1995). Nevertheless, both of them

significantly decreased exercise- and isoproterenol-induced tachycardia in conscious dogs (Djandjighian et al., 2000).

The inotropic effect is one of important concerning points of using the antiarrhythmic drugs in patient with heart diseases. Amiodarone and dronedarone unchanged LV functions; including LV dP/dt, ejection fraction (EF), fractional shortening (FS) (Djandjighian et al., 2000). Likewise in anesthetized pigs, dronedarone did not alter cardiac contractility measured by LV dP/dt (Sobrado et al., 2013).

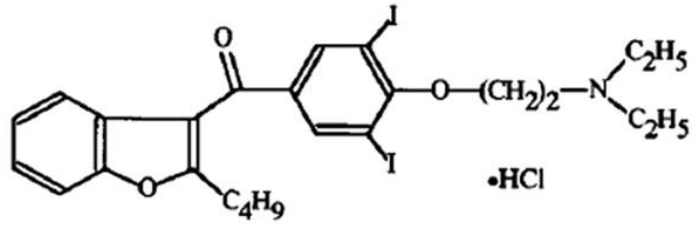
Amiodarone is one of the most potential rhythm control agents of AF. However, it has several extracardiac side effects (see more detail below at the topic of adverse effects), while dronedarone has fewer side effects for long term treatment. Nevertheless, dronedarone has unclear proarrhythmic issue that it could induce Torsade de Pointes (TdP). There was a case report showed TdP after a patient started dronedarone treatment for several months. They discussed in the report that TdP may be caused by drugs interaction between digoxin and dronedarone used in heart failure patients (Huemer et al., 2015). However, some study found that dronedarone would not increase incidence of TdP (Verduyn et al., 1999). The major contraindication of dronedarone treatment is high mortality in patient who had heart failure with permanent AF and major vascular problems (Connolly et al., 2011).

2.4 Adverse Effects

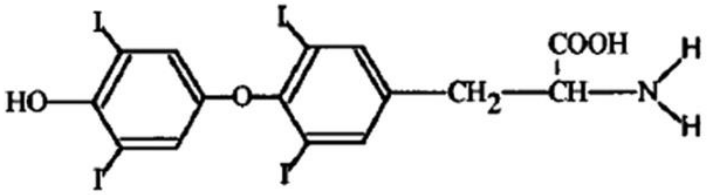
2.4.1 General adverse effects

Amiodarone has adverse effects on various organs for the long-term usage, for instance thyroid glands, liver, gastrointestinal tract, lungs, cornea, and skin. Some effects are dose-dependent and some are related to the drug structure (Harris et al., 1983). Photosensitivity is a general adverse effect that could be found in patients who received amiodarone, although sun screen or dosage reduction can diminish the effect (Harris et al., 1983). Nausea and loss of appetite can occur at the loading phase and disappear afterward. Patients may experience constipation, due to alteration of bowels in long term treatment (Harris et al., 1983). Thyroid dysfunction is a major concerning that usually be monitored in patients who started amiodarone treatment. Either hyperthyroidism or hypothyroidism can occur in long-term treatment (this topic will be descripted below in thyroid hormone issue). In 2009, Shalaby tried to manage thyroid hormone effects of amiodarone by adding carbamazole and prednisolone to amiodarone treatment. It improved rat thyroid follicular histology when compared to amiodarone treatment alone (Shalaby, 2009). Increasing of hepatic enzymes could also occur in patients treated with amiodarone. Pulmonary toxicity might be found in amiodarone treated patients, leading to decreasing capacity of carbonmonoxide diffusion (D_LCO). Moreover, corneal microdeposits cases were reported as well (Magro et al., 1988). Reduction the maintenance dose is recommended in these cases.

Dronedarone was deiodinated from the parent compound to avoid adverse effects of thyroid dysfunction but it still possessed the multichannel blocking and antiarrhythmic effects. On the other hand, the other adverse effects may be occurred. For example, liver toxicity and abnormal renal function (Naccarelli et al., 2011). Creatinine clearance was reduced significantly, approximately 18 % in healthy man with chronic oral dronedarone treatment compared to placebo group. Dronedarone caused serum creatinine increasing due to partially inhibition of organic cation transporter system, but not by direct renal function failure (Tschuppert et al., 2007).



Amiodarone (MW=682)



Thyroxine (MW=777)

Figure 3 Chemical structures and molecular weights of amiodarone (upper) and thyroxine (lower) (Vassallo and Trohman, 2007).

2.4.2 Thyroid dysfunction effect

Amiodarone structure has two iodine molecules. This is similarly to thyroxine (T_4) (figure 3) that amiodarone could produce adverse effects including abnormal thyroid hormone levels (Vassallo and Trohman, 2007). Amiodarone contains iodine 37% by weight (Harjai and Licata, 1997). The maintenance daily dose is 200 - 600 mg per day which is excessive daily iodine intake requirement of 0.2 – 0.8 mg per day by 75 - 225 mg per day (Markou et al., 2001). Dronedarone has no iodine molecule on its chemical structure. Theoretically, it would not produce thyroid dysfunction. The major form of thyroid hormone in blood stream is T_4, while 3,5,3'-Triiodothyronine (T_3) is the active form. T_3 affects heart functions by increase heart rate, contractility, cardiac output, and decreased systemic resistance (Klein and Ojamaa, 2001). The cardiomyocyte has T_3 transport proteins on the cell membrane specifically (Everts et al., 1996). T_3 could change the gene transcription resulting in changing cardiac function. Therefore patients with hyperthyroidism have T_3 – induced increasing of

contractility and diastolic function. T_3 can increase phospholamban, sarcoplasmic reticulum protein and calcium ATPase expressions in cardiomyocytes (Harjai and Licata, 1997). Moreover, amiodarone can inhibit conversion of T_4 to T_3 by inhibition of type 1 and 2 deiodinase (Harjai and Licata, 1997). It also can suppress thyroid hormone synthesis and secretion as well. In early phase of amiodarone treatment, serum T_4 might be high, while serum T_3 might be lower by 20-25%, then serum T_4 would decrease afterward (Wiersinga, 1997). Also, there was a report that T_3 was decreased by 5-20 % in patients with amiodarone therapy (Harjai and Licata, 1997). In other studies, chronic amiodarone treatment increased both plasma thyroid hormones, T_3 and T_4 significantly in rats, whereas chronic dronedarone treatment did not change thyroid hormone level (Chatelain et al., 1995; Pantos et al., 2002). Amiodarone treated patients were often be found abnormal result of thyroid function test, either AIT or AIH (Martino et al., 2001). However, incidence of AIH is higher due to iodine excess or the Wolff–Chaikoff effect. AIT could be found either, but fewer chance (Hofmann et al., 2008). The prevalence of thyroid dysfunction in patients treated with amiodarone was higher in elderly compared with those of younger patients (Hofmann et al., 2008).

2.5 Heart rate variability

HRV is a method to detect the autonomic nervous system (ANS) balancing which influences cardiac rhythm. HRV index is wildly used to predict mortality rate in patients with cardiovascular and extra-cardiovascular diseases, for instance heart failure, diabetes, stroke, and Alzheimer's disease. Patients with reduced HRV related to higher adverse events and risk of mortality due to unbalancing of sympatatic and parasympathetic system in any diseases (Vanderlei et al., 2009). HRV was introduced to detect therapy responses in ICU patients (Winchell and Hoyt, 1996). Currently in veterinary field, HRV has been increasingly used to investigate sympathovagal balance associated to physically and systemically disorders. Normal cardiac rhythm or respiratory sinus arrhythmia is usually irregular rhythm but not symmetrical pattern, due to balancing of autonomic nervous system or sympathovagal tone.

However, changing of heart rate mostly causes by vagal activity (Malliani et al., 1995). The concept of HRV analysis is to measure heart rate in details of beat-to-beat interval behavior. There are 2 useful indexes to investigate HRV; time domain and frequency domain.

Time domain index is a statistical analysis of HRV. The results is analyzed from every normal RR intervals or NN intervals, for example standard deviation and mean of NN intervals (Vanderlei et al., 2009). NN interval data is analyzed from long duration of ECG monitoring, for example 24 hours Holter monitor or telemetry, then calculated to time domain HRV. The time domain HRV requires much more NN interval data than frequency domain due to the equations are aim for averaging. For instance pNN50 = (NN50 count) / (total NN count). Otherwise, frequency domain index is broadly used to determine balancing of ANS, but required shorter duration of ECG data. This technique has been categorized into 3 - 4 frequency lengths, which are ULF, VLF, LF and HF.

HF represents the parasympathetic regulation and refers to respiratory effect on heart rate which influences respiratory sinus arrhythmia pattern (Berntson et al., 1997). In human, the range of HF is between 0.15 and 0.40 Hz. and LF band is set range between 0.04 and 0.15 Hz., relating to baroreflex. (Task-Force., 1996; Berntson et al., 1997) However, regulation of LF is still questioned, it possibly may also link to sympathetic regulation. Moreover, the VLF and ULF components are associated with thermoregulation and kidney function especially, renin angiotensin aldosterone system (Task-Force., 1996; Berntson et al., 1997). The studies of HRV have shown that only HF and LF are mostly significant related to the cardiovascular system. In addition, the low frequency to high frequency components ratio (LF/HF) was used as a parameter of sympathetic regulation of heart rate (Manzo et al., 2009) or a representation of sympatovagal balance (Task-Force., 1996; Berntson et al., 1997). Additionally, changing of HRV patterns associates with alterations in health status. The high HRV can indicate better adaptation of ANS and good prognosis for many disorders (Vanderlei et al., 2009).

Currently, there was no standardization for frequency band range in rabbits. Some researchers used the same range as human (Manzo et al., 2009) and some used the different ranges (Ronzhina et al., 2010). García-González and coworkers studied on frequency bands of HRV in Sprague-Dawley rat model for application to other animal models. They suggested to set the total spectral range at 95 percentile of maximal frequency, LF band as minimum frequency at 5% of power spectrum to 95% maximal frequency and HF as 95% of maximum spectral power to 99.9 percentile of 95% maximum frequency (García-González et al., 2011).

Furthermore, the study of HRV must study *in vivo* only because of the intact nervous system as can be seen in the study in isolated rabbit hearts HRV that shown random HRV pattern and fluctuations unlikely to intact rabbit pattern, due to denervation of the autonomic nervous system (Frey et al., 1996). There were a few studies about HRV with amiodarone treatment; intravenous amiodarone immediately increased HRV in rats, i.e. increasing vagal activity and reducing sympathetic activity significantly (Dias Da Silva et al., 2002a; Dias da Silva et al., 2002b). The study of European Myocardial Infarct Amiodarone Trial (EMIAT) shown prophylactic treated by amiodarone in patients with myocardial infraction who had HRV depression, which standard deviation of NN intervals (SDNN) < 50 ms led to HRV improvement with mortality rate reducing (Malik et al., 2000). According to the previous research results, amiodarone could increase HRV and decrease mortality rate. There is a possible advantage for using amiodarone to treat arrhythmia, whereas dronedarone has not been studied on HRV yet.

2.6 Echocardiography

2.6.1 Standard echocardiography

Transthoracic echocardiography is a non-invasive method to examine cardiac performance. Cardiac contractility is one of the major cardiac functions, which LV contractility can represent the global function due to its majority mass. There are many techniques to evaluate cardiac contractility. Standard echocardiography is an initial routine in clinical and experimental studies for over decades. The technique

can provide systolic function index from the right parasternal short axis view of the 2D mode guided M-mode at the papillary muscle tips. During diastole and systole, LV ejection fraction (EF), fractional shortening percentage (FS), pre-ejection period (PEP) and pre-ejection period to of ejection time ratio (PEP/ET) can be measured. The PEP/ET ratio refers to systolic performance with heart rate independent (Talley et al., 1971).

Doppler echocardiography was invented to examine additional information on cardiac performance. There were 2 main types of Doppler; hemodynamic Doppler and tissue Doppler imaging (TDI). TDI was independent to preload and afterload compared to classic Doppler. These both techniques can evaluate regional myocardial function. For instance, myocardial performance index or Tei index, and isovolumic contraction time (IVCT) (Figure 2). Additionally, the PEP is comparable to IVCT when both aortic and mitral valves are closed and LV forces pressure to against the aortic pressure.

2.6.1 Speckle tracking echocardiography

Speckle tracking echocardiography (STE) technique is an innovation technique. It is more sensitive for detection of early myocardial infarction in patients than standard echocardiography (Zhai et al., 2013). STE was derived from TDI to perform myocardial velocities and deformation due to limitation of TDI, which is angle dependent. Furthermore, cardiac contraction and relaxation are not only longitudinal motion. In fact, they are mixed with longitudinal, radial and circumferential motions, simultaneously. It is like twisting of a towel. The apex rotates counterclockwise and the base rotates clockwise for ejection phase (figure 4). On the other hand, the apex is rebound with clockwise rotation during relaxation for sucking blood into the heart. Thereby, STE can solve the limitation of TDI in term of angle dependent.

Strain (St) is the percent changing of myocardial length or tissue deformation. It simply means how many percentages that the muscle shortens or lengthens compare to the original length. And the rate of length changing is strain rate (SR). It is the changing of tissue velocity between two points of myocardium.

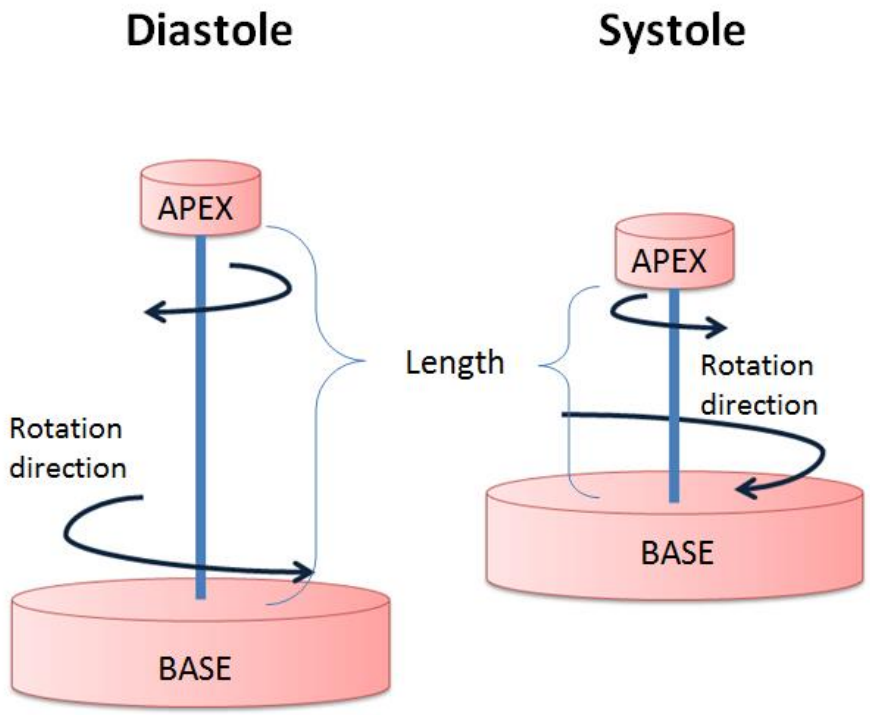


Figure 4 Left ventricular apex and base movement during the heart cycle

Myocardial strain has 3 directions; longitudinal, radial and circumferential planes (figure 5). When the heart contracts and relaxes, LV is shortened and elongated in longitudinal plane, thick and thin in radial plane and wide and narrow in circumferential plane. Additionally the largest area of the heart is LV which is mainly assessed the LV contractility or systolic function, such as EF, Tei index, and FS. These represent to the global heart functions. However, the nature of heart motions in each segments are not the same. Therefore, those above mention values of standard echocardiography could not express the heart function in each LV segments.

In STE, LV myocardium was divided into 17 segments, relating to the coronary arterial territories. There are six segments of parasternal short axis at basal plane, six segments of parasternal short axis at middle plane and five segments of parasternal short axis at apical plane (figure 6). The parasternal short axis of chordae tendinae or basal level is including basal anterior, basal anteroseptal, basal inferoseptal, basal inferior, basal inferolateral and basal anterolateral segments. The parasternal short axis at papillary muscle or middle level contains mid anterior, mid anteroseptal, mid interoseptal, mid inferior, mid inferolateral and mid anterolateral myocardial segments. And the last one is parasternal short axis at apical level, which is apical anterior, apical septal, apical inferior, apical lateral and apex segments (figure 6).

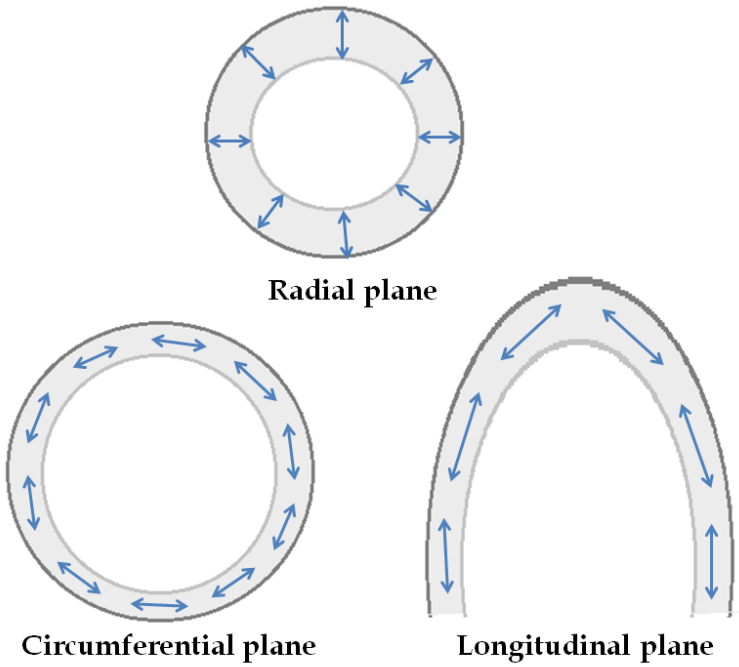


Figure 5 The 3 directions of myocardial strain; radial, circumferential and longitudinal planes.

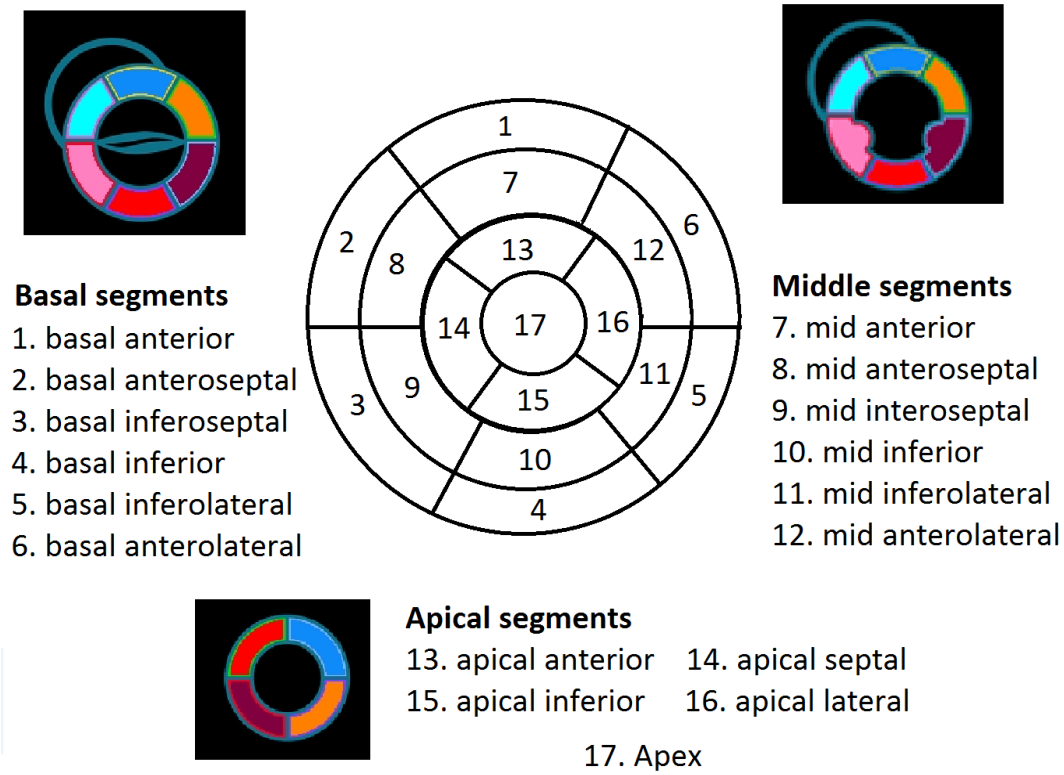


Figure 6 The 17 left ventricular myocardial segments related to coronary arterial territories.

2.7 A rabbit model and cardiovascular research

Cardiovascular disease is one of the major causes of mortality in humans. Therefore, many animal models were developed to represent cardiovascular diseases and related to human. Due to variations in heart properties among species, the specific animal model must be chosen to match with the human cardiovascular diseases. Currently, there are such none animal model that can represent perfectly as the human heart. Small animals such as rats, mouse and rabbits have been used widely in cardiovascular studies. They are easy to handle, lower management cost, less regulated by ethical agency and homogeneous genetic than large animals.

New Zealand white rabbit is wildly used for cardiovascular study related to human. Even though, there were slightly differences in calcium clearance, cardiac size and functions between human and rabbit. Rabbit shares more resemblance to human heart compared to mouse and rats. For example, rabbit heart rate (155 – 360 bpm) was significantly closer to human than small rodents i.e. mice heart rate is 310-840 bpm and rat heart rate is 250-493 bpm. Rabbit myocardial function is not limited when assess *in vivo* or *ex vivo* such as echocardiography, hemodynamic catheterization, electrocardiography and magnetic resonance imaging. These methods are clinical and experimental routine in rabbits now a day. Moreover, the expression of bata-MHC in rabbit ventricles was 88% to > 95% (James et al., 2005), which is quite similar to human bata-MHC expression (>90-95%) (Miyata et al., 2000; Reiser et al., 2001). Additionally, SERCA and NCX in rabbit influence calcium removal activities approximately 70-74% and 23-28%, respectively (Bassani et al., 1994; Puglisi et al., 1996). These numbers are similar to those human's SERCA and NCX activities, which are 76% and 24%, respectively (Piacentino et al., 2003). Furthermore, cardiac contraction and relaxation kinetics between human and rabbit are also more similar than those of small rodents; the rabbit's kinetics is 2-3 times faster than human whereas small rodents are 4-12 times faster. There is still discussion about effective size of the heart per body weight between animal models compare to human. Interestingly, rabbit heart effective size is more similar to human. Moreover, patterns of ventricular fibrillation in rabbit is more resemble to human compared to dogs and pigs (Panfilov, 2006). As a consequence, a rabbit model is better to reflect human heart than smaller animal models.

CHAPTER III
MATERIALS AND METHODS

3.1 The experimental protocol

The present study protocol was approved by the institutional animal care and use committee (IACUC), Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand, and the protocol number is 1531061. The animal use protocol is in the title "Effects of amiodarone and dronedarone on heart rate variability, cardiac contractility, and thyroid hormone levels in Rabbits".

Sixteen male New Zealand white rabbits (*Oryctolagus cuniculus*), weighing between 1.5 to 2.5 kilograms, were purchased from the Department of Animal Husbandry, Faculty of Veterinary Science, Chulalongkorn University. The rabbits were divided into 2 groups equally; amiodarone treated group and dronedarone treated group.

The rabbits were housed in the stainless steel rabbit housing unit with 2 animals per cage (size 24 inches wide x 48 inches long x 14 inches high). The rabbits were fed by a commercial rabbit diet through stainless J feeders and provided water by gravity fed water nipples connected to bottles, ad-libitum. The animals were enriched with proper among of fresh fruits (e.g. apple, carrot and strawberry) and hay to provide good quality of life. The light cycle of 12:12 hours was set with light cycle between 6 am and 6 pm and room temperature at 25 degree Celcius.

The present protocol were divided into 3 periods including,

3.1.1 The training period; this period had no any treatment involved, starting form Day (-)6 to Day 0 (figure 7). In this period, 2 rabbits were placed together and trained to stay inside acrylic rabbit restrainers for 1 hour daily on the propose to record conscious electrocardiograms on day (-)1, 6 and 13 of the protocol.

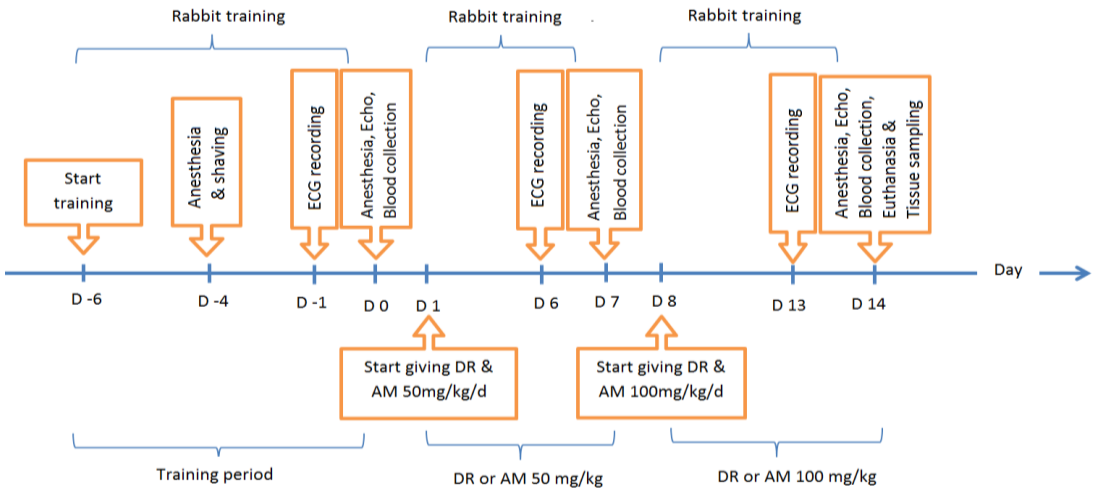


Figure 7 The experimental protocol timeline of the present study

On Day (–)4, rabbits were anesthetized with thiopental sodium (Anesthal, JAGSONPAL Pharmaceuticals, India) at a dose of 20 mg/kg, injected to the marginal ear vein. The rabbits were shaved by clippers at both left and right lateral chest area, preparing the skin for electrode attachment and echocardiographic evaluation. After fully recovery, the rabbits were return to their cages.

On Day (-)1, rabbits were placed to stay inside the restrainers and recorded ECG (PowerLab 16, ADInstruments, New Zealand) for an hour. After 1 hour, they were returned to their cages and given fruit and hay for enrichment.

On Day 0, rabbit diet was withheld approximately 3 hours before starting the experiment. The rabbits were lightly anesthetized with ketamine (CALYPSOL®, Gedeon Richter LTD., Hungary) at a dose of 17 mg/kg mixed with xylazine hydrochloride (X-Lazine, RXV, USA) at a dose of 4 mg/kg, intramuscularly (Pelosi et al., 2011) for immobility state. They were allowed breathing spontaneously and monitored vital sign by the real-time ECG during echocardiographic performing. An ultrasound machine (Mindray M9, Mindray, China) was used to obtain transthoracic echocardiograms. Standard 2D, M-mode, Doppler echocardiography, and STE were obtained either left or right sides for baseline values. After that, blood samples were collected for CBC and blood chemistry analyses. After fully recovery, the animals were return to their cages.

3.1.2 The treatment period 1; animals were given amiodarone (Cordarone®, Pfizer, NY, USA) or dronedarone (Multaq®, Sanofi Aventis, Paris, France) at a dose of 50 mg/kg/day (AM50 and DR50, respectively) daily from Day 1 to Day 7 of the protocol (figure 7). Before starting the treatment, the animals were weighed and then the dosages of the drugs were calculated. Then the drugs were mixed with propylene glycol (see drug preparation for more detail below). After gavaging the drugs to rabbits for 4 hours, the rabbits were brought to the experimental room and trained to stay inside the restrainer for an hour daily.

On Day 6, the rabbits were placed to stay inside the restrainers and recorded ECG for an hour. After 1 hour, they were returned to their cages and given fruits and hay for enrichment.

On Day 7, Rabbit diet was withheld approximately 3 hours before starting the experiment. The rabbits were lightly anesthetized with ketamine mixed with xylazine, then echocardiograms were obtained afterwards, and blood samples were collected again as values of the period of AM50 and DR50.

3.1.3 The treatment period 2; animals were given amiodarone or dronedarone at a dose of 100 mg/kg/day (AM100 and DR100, respectively) daily from day 8 to day 14 of the protocol (figure 7). After giving the drugs for 4 hours, the rabbits were brought to the experimental room and trained to stay inside the restrainer for an hour daily.

On Day 13, the rabbits were placed to stay still inside the restrainers and recorded ECG for an hour. After 1 hour, they were returned to their cages and given enrichments.

On Day 14, the last day of the protocol. Rabbit diet was withheld approximately 3 hours before starting the experiment. The rabbits were lightly anesthetized with ketamine and xylazine. After that echocardiograms were obtained, and blood samples were collected as values of the period of AM100 and DR100. Finally, the animals were given Thiopental sodium at a dose of 150 mg/kg, injected into the marginal ear vein for euthanasia and confirmed by heart removing.

3.2 Drug preparation

Amiodarone and dronedarone tablets were individual grinded by a mortar and a pestle before mixed with propylene glycol (Propylene Glycol B.P., VIDHYASOM CO., LTD, Thailand) with the ratio of 400 mg. of powdered drug to 10 ml of solvent to be the 40 mg/ml concentration for the treatment period 1 (day 1 to day 7) of AM50 and DR50, and the ratio of 800 mg. of powdered drug to 10 ml of propylene glycol to be the 80 mg/ml concentration for the treatment period 2 (day 8 to day 14) of AM100 and DR100.

3.3 Gavaging procedure

The drug administration in the present study was directly gavage into the stomach. The rabbits were placed inside the restrainer before gavage. Nasogastric feeding tubes (8 - French size (2.7 mm.), 20 inched lengths) were used with a safety connection plug that was marked with a permanent pen for the approximately length of the distance between rabbit's mouth and stomach. After that the animal mouth was closed, and the tube was inserted starting from the corner of the stable closed mouth passing through esophagus until reached the marked length. The outside-end of the tube was checked by dipped water before injected the prepared drug and followed by 5 ml water.

3.4 Electrocardiographic recording procedure

The animal was attached with 3 ECG electrode self-adhesive patches on the left side of the chest (figure 8). The patches were covered with stretchable adhesive tape (Fixomull® stretch, BSN medical, United Kingdom), after connected electrode with ECG cables. Finally, the chest was concealed with elastic bandage (Coban™, 3M, United States of America) to prevent the ECG cable movement. The cables were connected with an amplifier (Dual Bio Amp, ADInstruments, New Zealand) and an A/D converter (PowerLab 16, ADInstruments, New Zealand). The rabbit was placed inside the restrainer during ECG recording to obtain the conscious electrocardiograms with a commercial program (PowerLab chart 8, ADInstruments, New Zealand) for an hour.

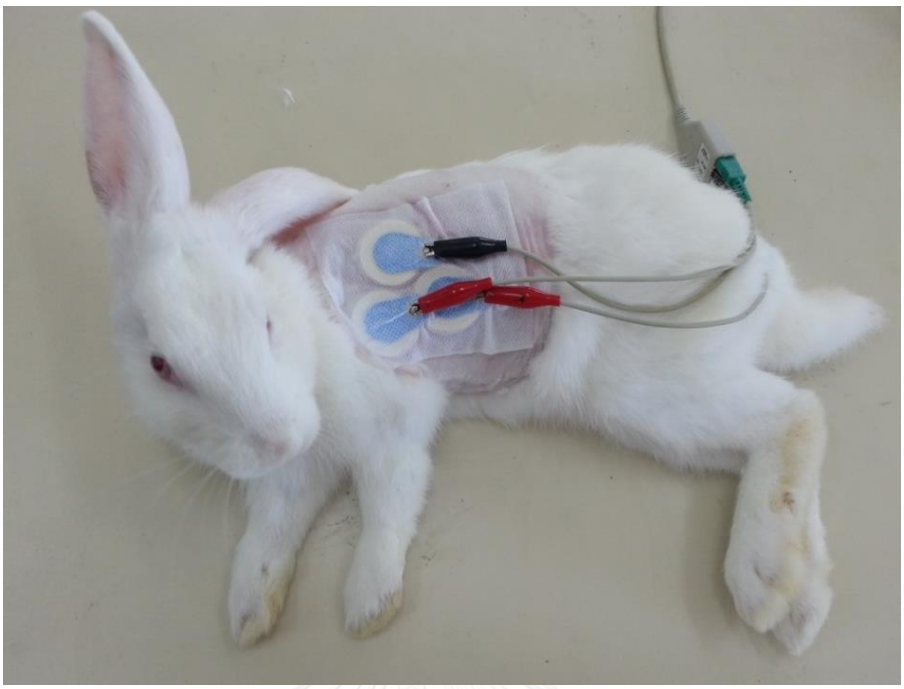


Figure 8 The ECG electrode attachment on the left-side of a rabbit covering with stretchable adhesive tape and connecting to ECG cables

Figure 9 A rabbit after covering electrode patches and cables with elastic bandage in the restrainer

3.5 Heart rate variability analysis

HRV analysis required a few minutes of stable ECG tachogram that excluded artifacts, unstable waves and ectopic beats. The tachogram contained 512 normal consecutive RR intervals (NN interval), which were used for frequency domain analysis of HRV. The HRV analysis was performed offline, and the graph of frequency domain was automatically generated using the Fast-Fourier Transformation (FFT) algorithm. The analysis program was set for the rabbit species. Therefore, the frequency bands were defined manually to 0.00 to 0.04 Hz. for VLF band, 0.04 to 0.5 Hz. for LF band, and 0.05 to 2.0 Hz. for HF band (modified from Ronzhina et al., 2010).

3.6 Echocardiographic performing and measurement procedures

3.6.1 Standard echocardiography

Standard echocardiograms were obtained from either right or left parasternal planes. Rabbits were anesthetized and placed lateral recumbency on a special table which had proper holes for placing the ultrasound probe. ECG flat-jaw electrode clips (EL6304A model, Mindray, China) were clamped on rabbit's limbs. The RA and LA labeled clips were attached to the right and left forelimbs respectively, and the LL labeled clip was placed on the left hind limb.

The right parasternal short-axis views were approached by placing the probe (Phased array P10-4s, Mindray) at the cardiac notch located between sternum and intercostal space 3-5th. After the papillary muscle of right parasternal short axis in 2D mode was located, pictures in M-mode were obtained for cardiac dimension analysis. The measurement was applied offline. LV wall thickness in diastole and systole were manually measured for interventricular septum diameter during diastole (IVSd), left ventricular internal diameter during diastole (LVIDd), left ventricular posterior wall diameter during diastole (LVPWd), interventricular septum diameter during systole (IVSs), left ventricular internal diameter during systole (LVIDs), and left ventricular posterior wall diameter during systole (LVPWs) (figure 10). The end-diastolic volume

(EDV), end-systolic volume (ESV), stoke volume (SV), ejection fraction (EF), fractional shortening percentage (FS) and cardiac output (CO) were automatically calculated by formulas (Fig 11). Heart rate (HR) was computed from RR intervals of recorded ECG (figure 10). All the LV parameters of M-mode are provides formulas in the figure 11.

After that the probe was carefully fanned towards the heart base until the round shape of the aortic root had seen on the monitor of the 2D mode. M-mode pictures were captured for analysis of pre-ejection period (PEP) and ejection time (ET). PEP was measured from the beginning of the Q wave of ECG to the starting of the aortic valves opened. ET was defined as the interval between the aortic valves opened until closed (figure 12).

Myocardial performance index or Tei index, was obtained from the left parasternal view. The 5-chamber long axis was used to access the aortic outflow tract and placed the Doppler sampling window. Isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT) and ET were manually measured by the caliper of the program (figure 13). Then, Tei index was calculated by the followed equation (figure 14).

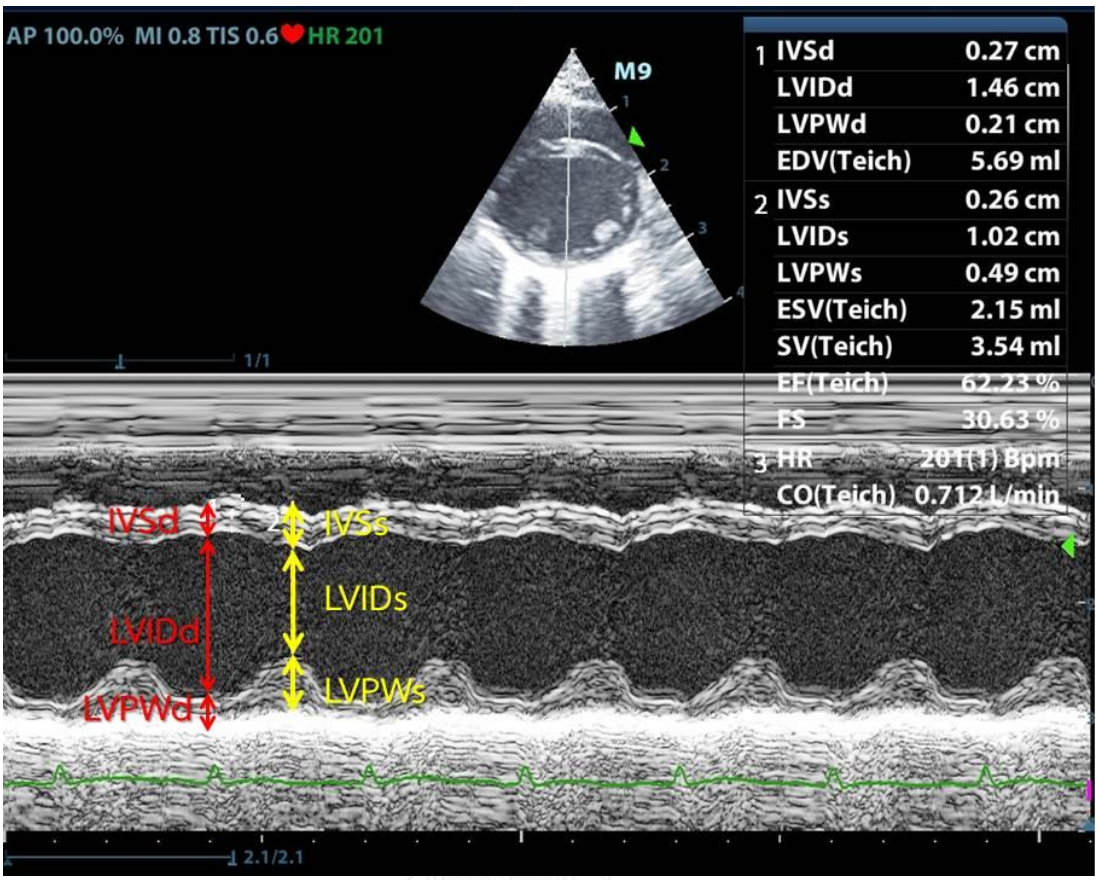


Figure 10 An example of right parasternal short axis view from M-mode at the papillary muscle tips and calculated values from the M9-package program

Abbreviations; IVSd = interventricular septum diameter during diastole, LVIDd= left ventricular internal diameter during diastole, LVPWd = left ventricular posterior wall diameter during diastole, IVSs = interventricular septum diameter during systole, LVIDs = left ventricular internal diameter during systole, and LVPWs = left ventricular posterior wall diameter during systole

$$\text{End-diastolic volume (EDV)} = \frac{7.0}{(2.4 + \text{LVIDd})} \times \text{LVIDd}^3 \quad \text{(ml)}$$

$$\text{End-systolic volume (ESV)} = \frac{7.0}{(2.4 + \text{LVIDs})} \times \text{LVIDs}^3 \quad \text{(ml)}$$

$$\text{Stroke volume (SV)} = \text{EDV-ESV} \quad \text{(ml)}$$

$$\text{Cardiac output (CO)} = \frac{\text{SV} \times \text{HR}}{1000} \quad \text{(L/min)}$$

$$\text{Fractional shortening (FS)} = \frac{\text{LVIDd - LVIDs}}{\text{LVIDd}} \times 100 \quad (\%)$$

$$\text{Ejection fraction (EF)} = \frac{\text{EDV - ESV}}{\text{EDV}} \times 100 \quad (\%)$$

Figure 11 Formulas of the left ventricular M-mode measurement with the units

Abbreviations; EDV = end diastolic volume, LVIDd Left ventricular internal diameter during diastole, EDS = end diastolic volume, LVIDs = Left ventricular internal diameter during systole, SV = stroke volume, CO = cardiac output, HR = heart rate, EF = ejection fraction, FS = fractional shortening

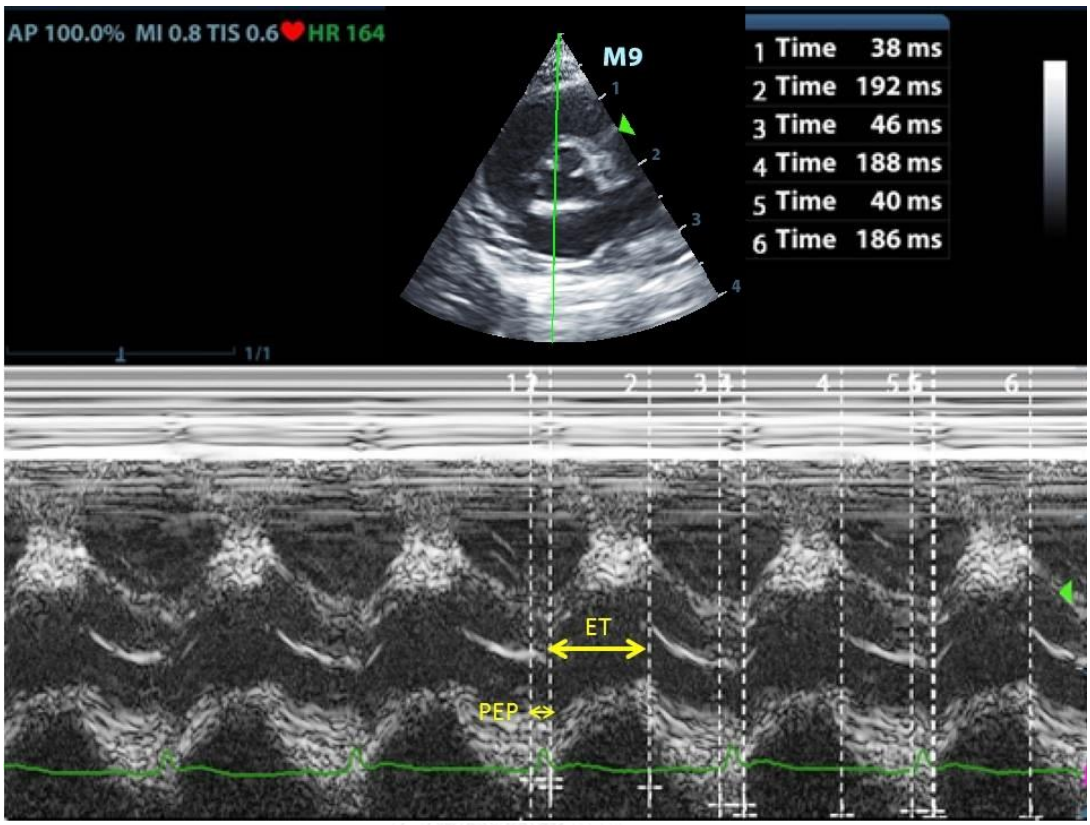


Figure 12 2D and M-mode pictures placing cursor at the aortic root of the right parasternal short axis view with measurements 3 consecutive beats of pre-ejection period (PEP) and ejection time (ET).

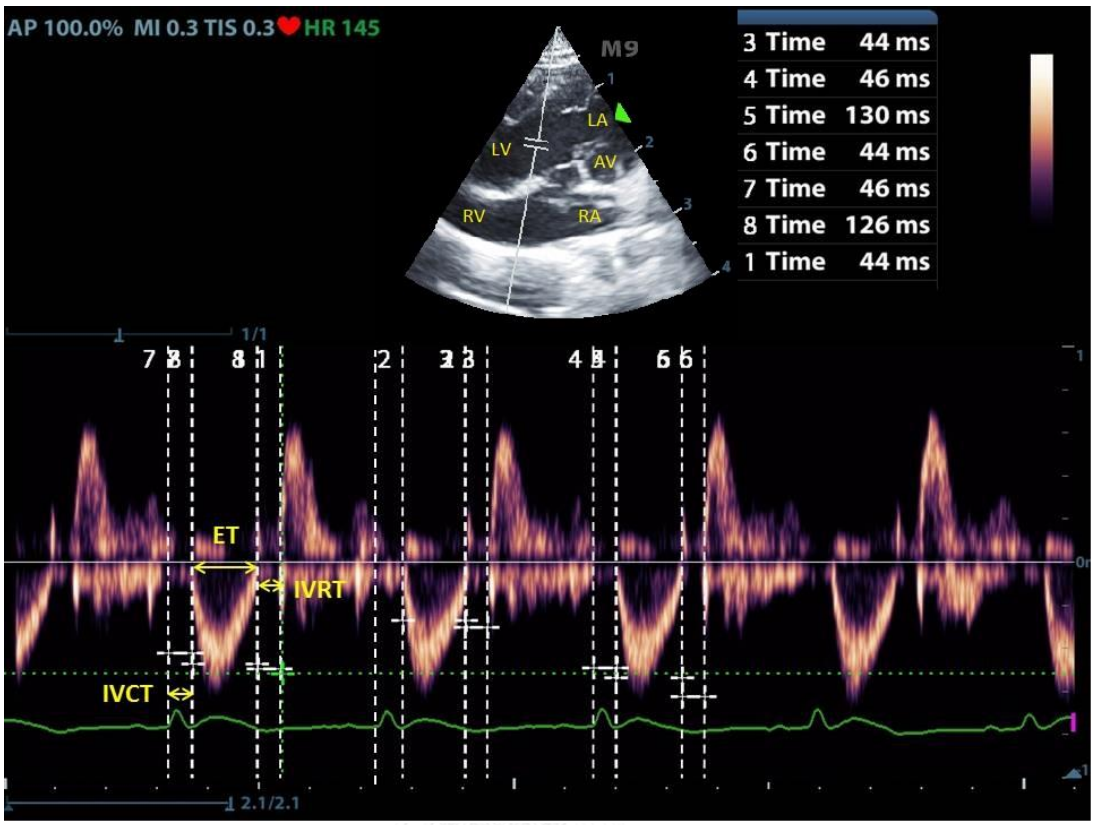


Figure 13 Pulse wave Doppler echocardiogram at the aortic outflow of the left parasternal apical 5-chamber long axis view with measurements of isovolumic contraction time (IVCT), ejection time (ET), and isovolumic relaxation time (IVRT).

The labels on the 2D picture; LA = left atrium. LV = left ventricle, AV = aortic valves, RA = right atrium and RV = right ventricle

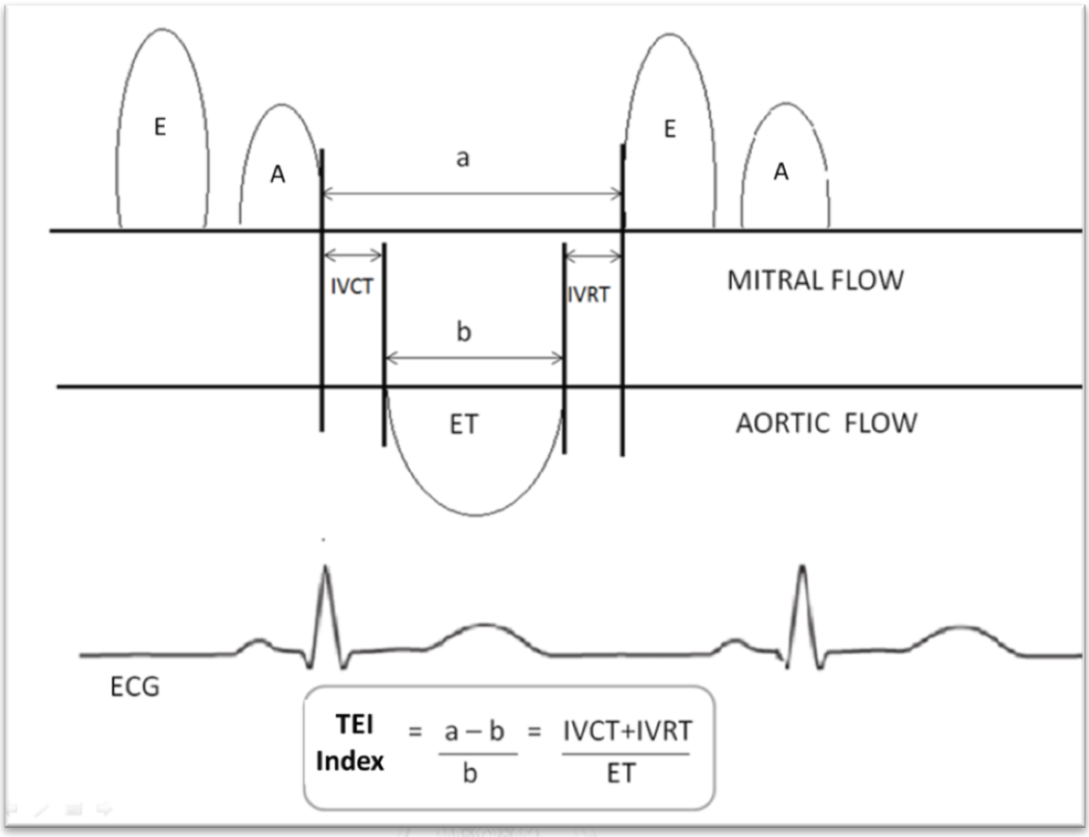


Figure 14 Drawing diagram from the pulse wave Doppler image to demonstrate the Tei index calculation; A = late diastolic filling, a = time interval from the end of A wave to the start of E wave of mitral inflow, b = left ventricular ejection time (ET) of aortic outflow, E = early filling, IVCT = isovolumic contraction time, IVRT = isovolumic relaxation time

3.6.2 Speckle tracking echocardiography

At the right parasternal short axis, LV 2D mode images were obtained for STE analysis at 3 myocardial levels, including chordae tendinae, papillary muscle and apex (figure 9). The ultrasound machine was set to save motion clip for 5 consecutive heart beats each time. Data analyses were performed offline, using the software package (Tissue tracking QA package, Mindray M9, China). Radial and circumferential of either St or SR parameters were computed with the program by choosing either parasternal short axis base (PSAXB), parasternal short axis middle (PSAXM) or parasternal short axis apex (PSAXAP) (figure 9) for the chordae tendinae, the papillary muscle and the apex levels respectively.

The circular marks were manually placed on the myocardium silhouette while the screen was stopped manually at the clearest part. Three consecutive beats were used for calculated variables. STE parameters were computed by the software package after proper setting and adjusting the marks. All St and SR values of either circumferential or radial planes are presented into line graph, bull's eye graphs and digital values of the 16 LV segments of all 3 short axis planes; basal, middle and apical planes (figure 15).

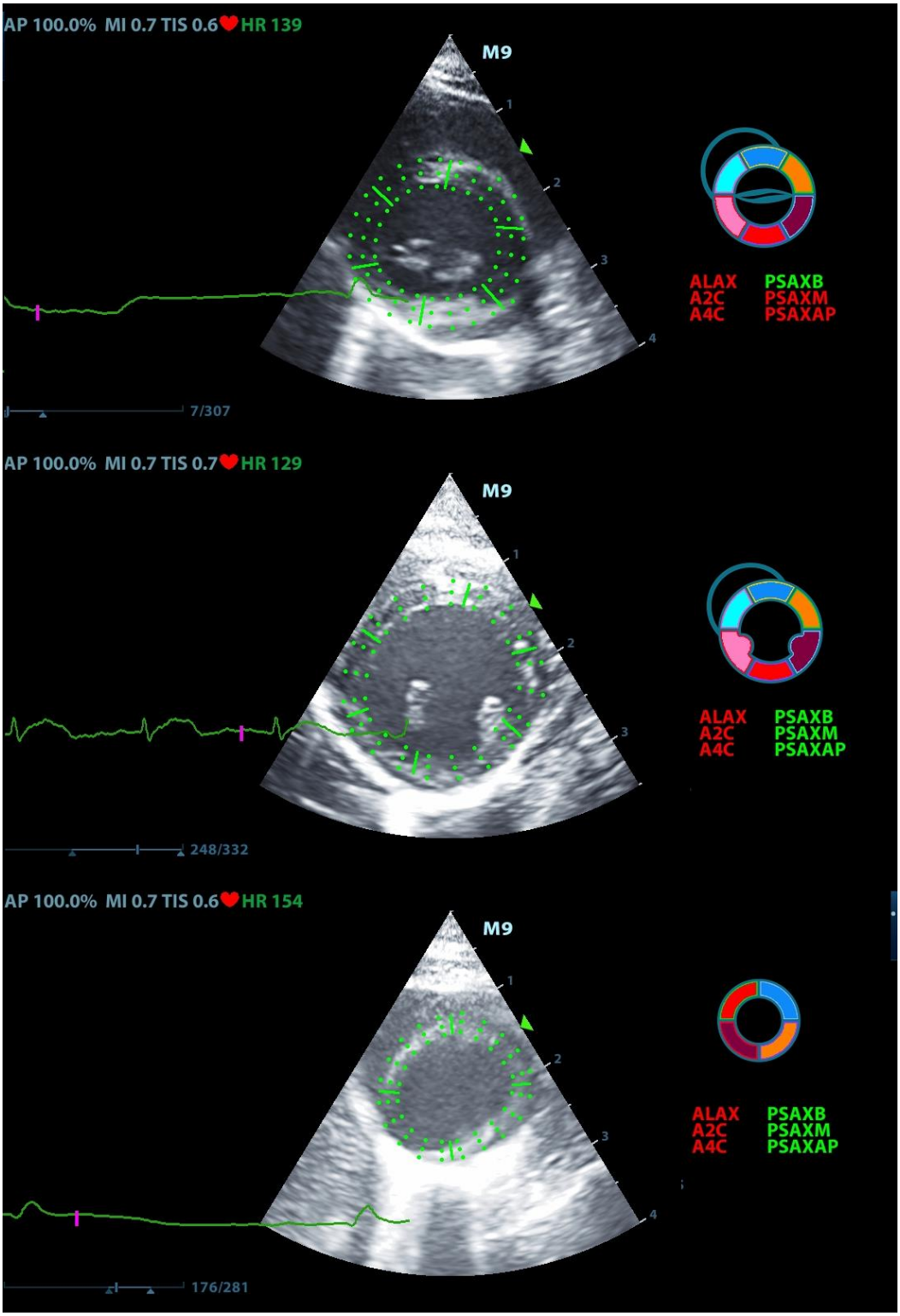


Figure 15 The tissue tracking QA image with circular marks placing on the myocardium silhouette from upper to lower; the basal (PSAXB), middle (PSAXM), and apical parts (PSAXAP) of the left ventricle.

3.7 Blood collection and analysis

Four milliliters of blood samples were drawn from the central ear artery using a 23 Gauge needle (Nipro Hypodermic 23G 1" Needle, Nipro Medical Corporation, NJ, USA) connected with a 5 milliliters syringe (Nipro Hypodermic 5 cc Syringe, Nipro Medical Corporation, NJ, USA). The blood sample was separated into a serum tube for 2 ml, a heparinized tube for 1 ml, and an ethylenediaminetetraacetic acid (EDTA) tube for 1 ml, before kept cool in an ice bucket.

Serum and heparined samples were collected using a refrigerated centrifuge with the 90° swing-out rotor (Universal Centrifuge 32R, HETTICH, Germany). The speed was set at 2,000 rpm, temperature was set at 4 degree Celsius and the total time was set for 10 minutes centrifugation.

Thyroid hormone levels, total T3 and total T4, were analyzed by the enzyme labeled chemiluminescent competitive immunoassay analyzer (IMMULITE ONE immunoassay system, Siemens, Germany). The tests required rabbit serum 150-300 µl per sample.

Blood chemistry test in the present study was analyzed for liver and renal profiles by an automated analyzer (Urit-8030 Automatic chemistry analyzer, URIT Medical Electronic Group Co., Ltd, China) with blood chemistry reagents (Stanbio Laboratory, USA). There were alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), total protein (TP), albumin, bilirubin, blood urea nitrogen (BUN) and creatinine (Cr). ALT and AST were analyzed by modified International Federation of Clinical Chemistry and Laboratory Medicine method and ALP was analyzed by P-nitrophenylphosphate Methodology. GGT was determined by Modified Szasz Methodology, and Bilirubin was analyzed by DCA (2,4-Dichloroaniline) Methodology. Total protein and albumin were measured by colorimetric tests of the Biuret Reaction and Bromocresol green method, respectively. Cr and BUN were analyzed by colorimetric tests of Jaffe reaction and modified Berthelot method, respectively.

Complete blood count (CBC) was analyzed by an automated hematology analyzer (Sysmex XT-2000i, Sysmex, Japan) with an EDTA blood sample. The results provided

red blood cells (RBC), hemoglobin, white blood cell (WBC) differential population and platelets. RBC and platelets were counted by the direct current detection method. Hemoglobin was detected by a non-cyanide method. WBC differential population was analyzed by fluorescent flow cytometry method.

3.8 Statistical analysis

All data were shown in Mean±SEM. The one way repeated measure ANOVA was used to analyze the data within group and the Student Newman-Keuls Post hoc test was used to examine differences among time periods. The differences between amiodarone and dronedarone groups at the same time were analyzed using the student t-test. Moreover, $p \leq 0.05$ was considered as a statistically significance.

CHAPTER IV
RESULTS

The present study was intended to evaluate HRV, cardiac contractility and thyroid hormone level in New Zealand white rabbits treated with amiodarone and dronedarone.

4.1 General conditions

4.1.1 Complete blood count monitoring

WBC counts among AM50, AM100, DR50 and DR100 were no significant differences from their baselines in either amiodarone or dronedarone treated groups, and there also were not different between amiodarone and dronedarone in any treatment periods (table 1).

RBC count in the amiodarone group were not significantly different among periods (p=0.055). Whereas, RBC counts in the dronedarone group at low and high doses (50 and 100 mg/kg/day, respectively) were decreased markedly compared to the baseline (p=0.02 and 0.028, respectively). The RBCs in the amiodarone group were significantly lowered than the dronedarone group after treatments both 50 mg/kg and 100 mg/kg (p=0.0327 and 0.0484, respectively) (table 1). Hemoglobin concentrations in amiodarone and dronedarone treatment groups did not reach statistical significances when compared to their baselines (p=0.17 and 0.31, respectively). Hematocrits of amiodarone and dronedarone treated groups were not changed significantly among periods, but hematocrits of the amiodarone group were lower than the dronedarone group after treatments both 50 mg/kg and 100 mg/kg (p=0.0269 and 0.036, respectively). Mean corpuscular volumes (MCV) remained unchanged among periods of the amiodarone group, but there was significantly increased after dronedarone treatment, DR50 and DR100, compared to the baseline (p=0.03 and 0.02, respectively). There was no significant difference of the MCV between amiodarone and dronedarone treated groups (table 1). Mean corpuscular hemoglobin (MCH) were markedly increased among periods in the amiodarone group

(p=0.005 and <0.001, respectively), while there was no change in the dronedarone group (table 1). Mean corpuscular hemoglobin concentrations (MCHC) among periods in the amiodarone group were comparable to the baseline, but there were significantly decreased in DR50 and DR100 compared to the baseline (p=0.01 and 0.01, respectively) (table 1).

Finally, platelet counts and mean platelet volumes (MPV) were not significantly differences in any periods of treatments compared to the baselines, and there were no differences between amiodarone and dronedarone treated groups (table 1). Nevertheless, all CBC values were in normal ranges.

4.1.2 Blood chemistry monitoring

In the present study, blood chemistry had been monitored for the liver and renal profiles of rabbits treated with amiodarone and dronedarone. AST and ALT were decreased by either AM100 (p=0.04 and 0.016, respectively), DR50 (p=0.039 and 0.016, respectively), and also DR100 (p=0.039 and 0.02, respectively) compared to their baselines. Another hepatic enzyme, ALP was significant increased by AM100 when compared to the baseline (p<0.001) and compared to the AM50 (p<0.001), while other biochemical tests; GGT, TP, Alb, TB, and DB remained unchanged (table 2).

Renal profile tests, BUN and Cr in both amiodarone and dronedarone treated groups were also no significant differences compared to their baselines, and between treatments in the same period (table 2). Nevertheless the blood chemistry values were in normal ranges.

Table 1 Complete blood counts of the rabbits in amiodarone (n=8) and dronedarone (n=8) treated groups

Index	Normal range*	Mean±SEM					
		AM baseline	AM 50	AM100	DR baseline	DR 50	DR100
WBC (10^3/uL)	2.4-11.1	5.39 ±0.35	4.83 ±0.19	4.81 ±0.32	6.10 ±0.90	5.71 ±0.72	5.07 ±0.47
RBC (10^6/uL)	3.7-7.5	5.46 ±0.25	5.11^{1} ±0.15	5.17^{1} ±0.15	5.92^{a} ±0.18	$5.59^{b,2}$ ±0.13	$5.55^{b,2}$ ±0.10
Hb (g/dL)	10-12	11.06 ±0.48	10.50 ±0.31	10.70 ±0.31	11.69 ±0.31	11.36 ±0.27	11.33 ±0.23
Hct (%)	26.7-47.2	35.66 ±1.14	33.68^{1} ±0.94	34.66^{1} ±0.66	34.01 ±3.28	36.79^{2} ±0.84	36.76^{2} ±0.62
MCV (fL)	62-69	65.70 ±1.55	66.06 ±1.43	67.33 ±1.51	63.71^{a} ±0.93	65.91^{b} ±0.97	66.50^{b} ±0.98
MCH (pg)	19.5-21.5	20.29^{a} ±0.29	20.56^{b} ±0.32	20.71^{b} ±0.30	20.20 ±0.27	20.34 ±0.29	20.48 ±0.33
MCHC (g/dL)	29.8-37.0	29.94 ±1.34	31.19 ±0.44	30.86 ±0.55	31.74^{a} ±0.55	30.90^{b} ±0.57	30.80^{b} ±0.43
Platelet (10^3/uL)	111-796	491.88 ±54.06	474.38 ±32.90	427.88 ±28.39	435.13 ±33.95	403.88 ±49.96	437.50 ±15.82
MPV (fL)	6.5-8.3	7.16 ±0.15	7.09 ±0.15	7.44 ±0.17	7.09 ±0.14	7.25 ±0.16	7.15 ±0.17

Different letters (^{a,b}) within the same drug treatments represent significant differences among periods ($p<0.05$), Different numbers (^{1,2}) represent significant differences ($p<0.05$) of the same period between amiodarone and dronedarone treatments; WBC = white blood cell, RBC = red blood cell, Hb = hemoglobin, Hct = hematocrit. MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MPV = mean platelet volume, *Normal range from Isoquimen SL laboratory, Barcelona, Spain

Table 2 Blood chemistry profiles of the rabbits in amiodarone and dronedarone treated groups

Index	Normal range*	Mean±SEM					
		AM baseline	AM 50	AM100	DR baseline	DR 50	DR100
AST (IU/L)	13-40	25.58[a] ±3.43	22.20[a,b] ±4.99	14.69[b] ±1.17	27.89[a] ±5.19	18.18[b] ±1.90	16.16[b] ±1.52
ALT (IU/L)	33-81	45.58[a] ±4.99	42.04[a,b] ±4.32	36.28[b] ±4.13	61.33[a] ±8.14	46.91[b] ±3.80	45.00[b] ±4.02
ALP (IU/L)	29-490	152.46[a] ±10.10	160.04[a] ±10.85	196.89[b] ±9.34	162.16 ±20.03	172.39 ±23.87	172.44 ±19.99
GGT (IU/L)	0-14	10.43 ±1.13	11.46 ±1.69	10.43 ±1.33	12.29 ±1.53	11.70 ±1.14	11.04 ±1.14
TP (g/dL)	5.0-7.2	6.06 ±0.16	5.74 ±0.09	5.69 ±0.11	6.13 ±0.05	6.06 ±0.11	6.06 ±0.09
Alb (g/dL)	3.5-4.8	4.31 ±0.31	4.14 ±0.24	4.18 ±0.24	4.14 ±0.29	3.99 ±0.18	4.18 ±0.27
TB (mg/dL)	0.1-0.7	0.69 ±0.04	0.66 ±0.05	0.68 ±0.08	0.70 ±0.07	0.64 ±0.04	0.60 ±0.06
DB (mg/dL)	0.03-0.5	0.21 ±0.07	0.19 ±0.06	0.22 ±0.08	0.14 ±0.06	0.16 ±0.07	0.15 0.06
BUN (mg/dL)	8.3-17.5	15.66 ±0.66	13.34 ±0.67	14.06 ±0.98	16.24 ±1.08	14.95 ±1.03	14.65 ±1.26
Cr (mg/dL)	0.7-1.0	0.81 ±0.06	0.80 ±0.04	0.81 ±0.04	0.88 ±0.08	0.91 ±0.05	0.94 ±0.06

Different letters (a,b) within the same drug treatments represent significant differences among periods ($p<0.05$); AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; TP = total protein; Alb = albumin; TB = total bilirubin; DB= direct bilirubin, BUN = blood urea nitrogen; Cr = Creatinine, *Normal ranges are from Isoquimen SL laboratory, Barcelona, Spain

4.1.3 Thyroid hormone monitoring

In the present study, total T_3 levels were not changed significantly among periods in both amiodaone and dronedarone treated groups. However, total T_4 levels were significantly increased in amiodarone treated group after given at a dose of 50 mg/kg (p<0.001) and a dose of 100 mg/kg (p<0.001) as shown in table 3. On the other hand, T_4 were reduced significantly after treated with dronedarone at a dose of 100 mg/kg (p=0.01) but not at a dose of 50 mg/kg compared to its baseline. Moreover, the T_4 levels in the same treatment periods between both drugs were significantly differences (Table 3).

Table 3 Serum total T_3 and T_4 levels of the rabbits in amiodarone (n=8) and dronedarone (n=8) treated groups

Treatment	Mean±SEM	
	tT_3 (ng/dl)	**tT_4 (µg/dl)**
AM baseline	90.79±9.04	6.90±0.89[a]
AM50	96.74±9.73	11.63±0.66[b, 1]
AM100	80.20±7.27	12.23±0.59[b, 1]
DR baseline	83.20±14.62	6.30±0.63[a]
DR50	91.20±6.65	5.21±0.49[ab, 2]
DR100	100.43±11.1	4.53±0.46[b, 2]

Different letters ([a,b]) within the same drug treatments represent significant differences among periods (p<0.05), different numbers ([1,2]) represent significant differences *(p<0.05)* of the same period between amiodarone and dronedarone treatments.; tT_3 = total triiodothyronine level, and tT_4 =total thyroxine level

4.2 Heart rate variability

4.2.1 Heart rate

Amiodarone treatment at the dosage of 100 mg/kg was found to decrease heart rate significantly compared to the baseline (p=0.041). Dronedarone treatment at high dose (100mg/kg) was also reduced heart rate significantly when compared to the baseline and low dose (50 mg/kg) (p=0.004 and 0.005, respectively) (table 4). There was no significant difference of heart rate between amiodarone and dronedarone treatments within the same periods (Table 4).

Additionally, RR histograms showed the RR interval counting from each period of the present study, which the x-axis represent the RR interval (ms) and the y-axis represent the counting number of RR interval. The RR interval trends in the treatment period 1 and 2 of both treatment groups were longer compared to their baselines (figure 16), which might be associated with negative chronotropy (table 4).

4.2.2 Frequency domain analysis

The spectral analysis of frequency domain was demonstrated in the present study. Amiodarone and dronedarone treatments at dose of 100 mg/kg daily had significantly reduced the total power (p=0.014 and 0.014, respectively) and the LF component (p=0.035 and <0.001, respectively) compared to their baselines (table 4). While, the very low frequency and high frequency components were unchanged by neither amiodarone nor dronedarone. The ratio of LF/HF component (LF/HF), had been decreased at the dose of 100 mg/kg of amiodarone and dronedarone treatments when compared to their baselines with p=0.005 and 0.001, respectively. Moreover, the LF/HF ratio was also significantly reduced by dronedarone at the dose of 50 mg/kg (p=0.008). However, neither amiodarone nor dronedarone treatments at the same period had significant differences (table 4).

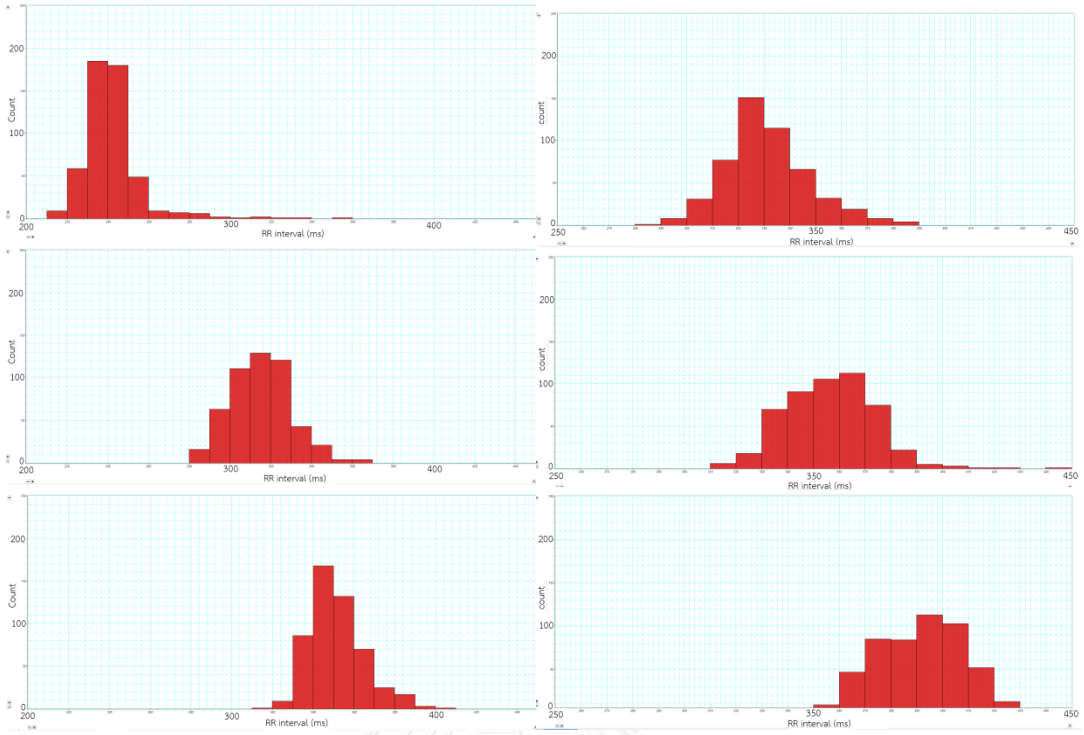


Figure 16 RR histogram represents the distribution of RR interval (ms) in the different treatment periods from the rabbit No. AM03 (left) and the rabbit No. DR06 (right) referred to their baselines (top), a dose of 50 mg/kg/day (middle) and a dose of 100 mg/kg/day (bottom), respectively.

Table 4 Heart rate and frequency domain analysis of heart rate variability from the conscious rabbits in amiodarone (n=8) and dronedarone (n=8) treated groups

Index	Means±SEM					
	AM treatment			DR treatment		
	Baseline	AM50	AM100	Baseline	DR50	DR100
Heart rate (BPM)	218.61[a] ±8.40	199.69 [a,b] ±14.49	192.21[b] ±7.12	207.86 [a] ±5.69	204.81[a] ±6.37	188.33[b] ±7.23
Total power (μs^2)	193.07[a] ±23.95	166.24[ab] ±17.64	139.37[b] ±18.57	216.08[a] ±23.08	182.13[ab] ±33.90	137.43[b] ±31.42
VLF (μs^2)	92.15 ±18.72	59.83 ±13.77	58.86 ±12.19	99.89 ±18.38	79.204 ±19.50	71.91 ±17.48
LF (μs^2)	86.89[a] ±11.85	78.88[a] ±10.08	52.46[b] ±6.19	92.26[a] ±11.32	71.30[a] ±15.33	37.03[b] ±8.18
HF (μs^2)	19.38 ±4.03	30.36 ±9.29	30.85 ±5.20	31.32 ±7.48	41.06 ±12.41	30.83 ±8.56
LF/HF ratio	5.39 [a] ±0.89	3.99[ab] ±0.83	2.32[b] ±0.65	3.80[a] ±0.64	2.28[b] ±0.54	1.54[b] ±0.24

Different letters ([a,b]) within the same drug treatments represent significant differences among periods ($p<0.05$); BPM= beat per minute, VLF = very low frequency component (0.00 - 0.04 Hz.), LF = low frequency component (0.04 - 0.5 Hz.), HF = high frequency component (0.5 - 2.0 Hz.), LF/HF ratio = ratio between low frequency and high frequency components

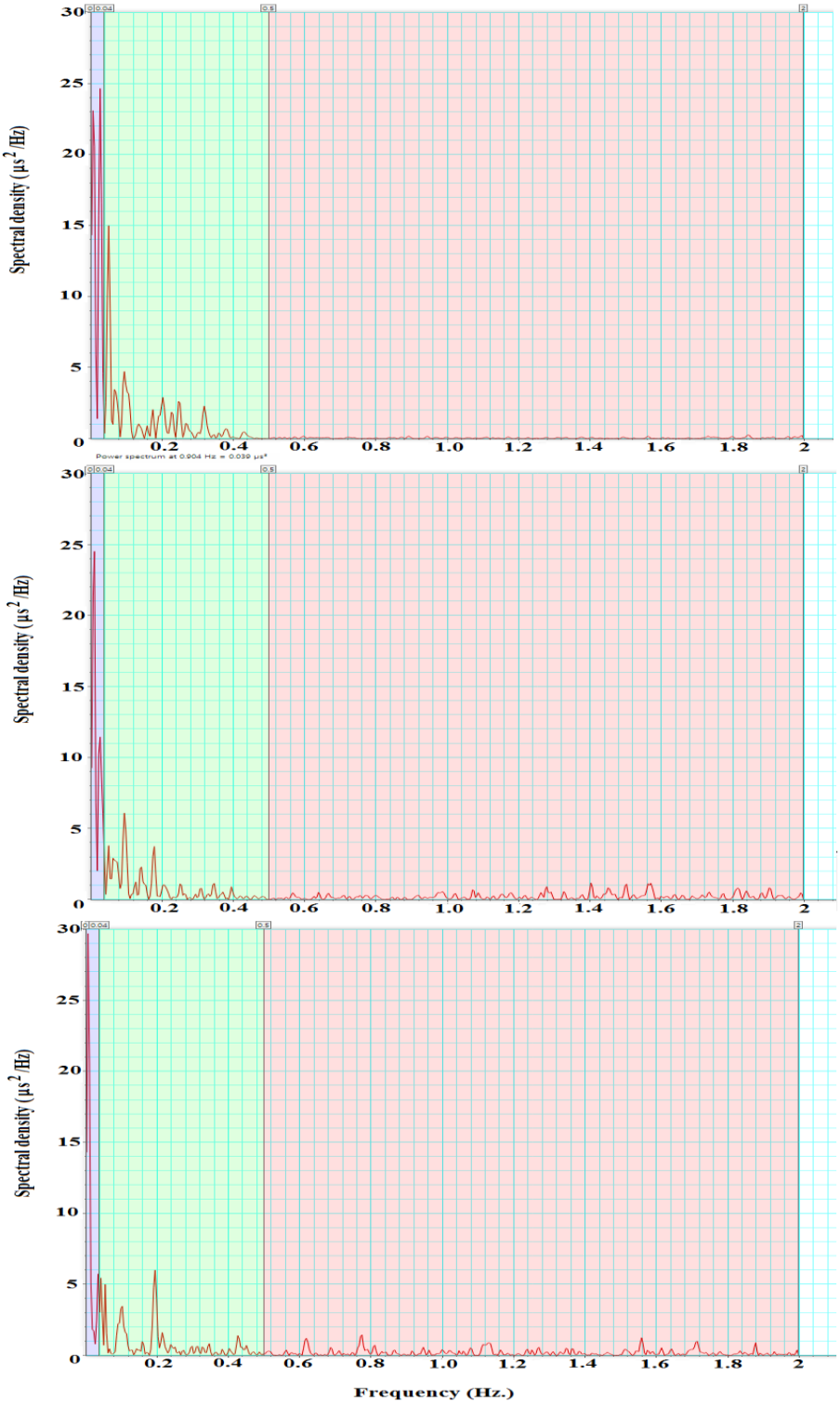


Figure 17 Power spectrum plots at different periods of the rabbit No. AM03 which shows the separated frequency bands; purple =very low frequency component, green = low frequency component, and red = high frequency component at the baseline (top), AM50 (middle) and AM100 (bottom)

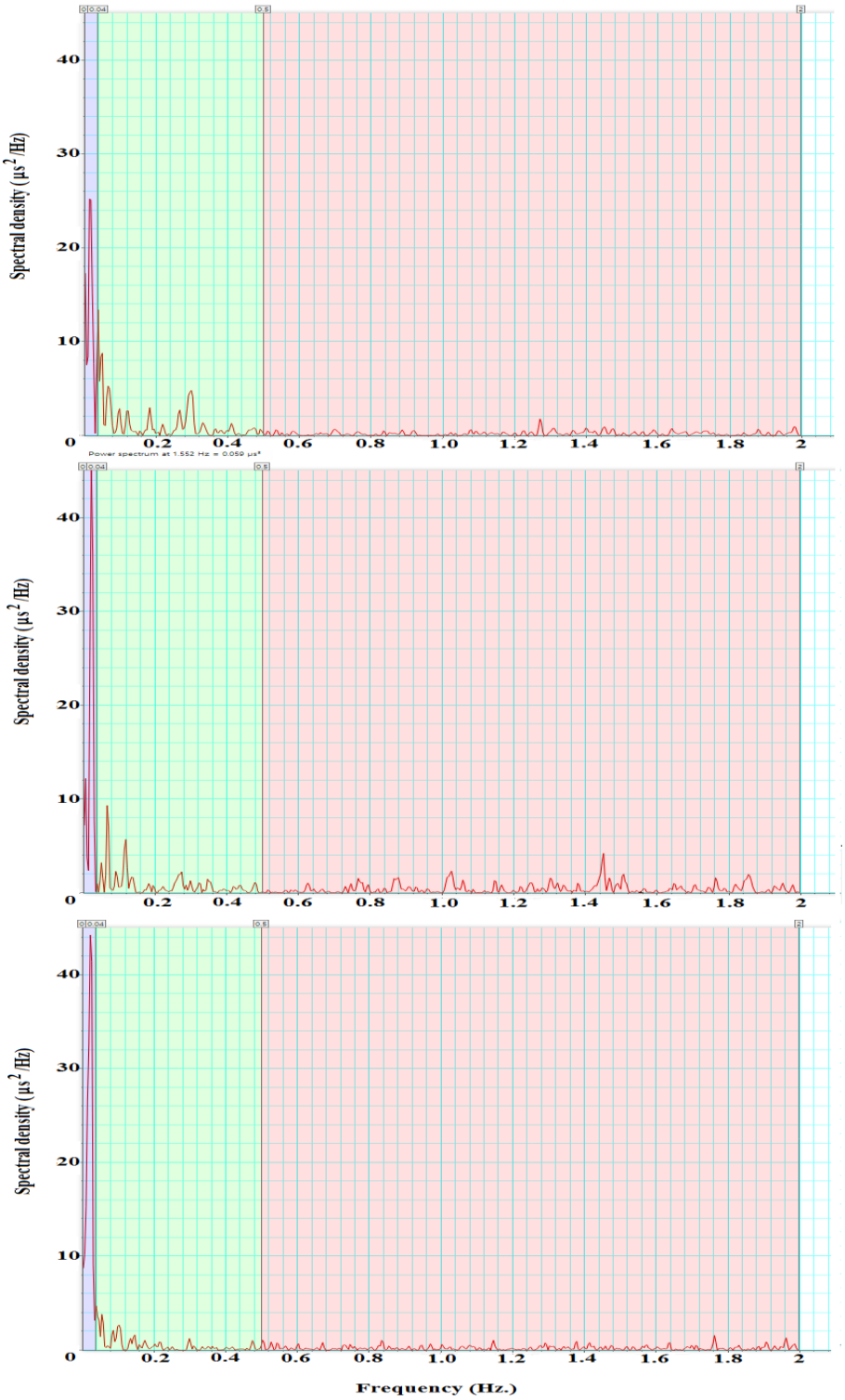


Figure 18 Power spectrum plots at different periods of the rabbit No.DR06 which shows the separated frequency bands; Purple =very low frequency component, Green = low frequency component, and Red = high frequency component at the baseline (top), DR50 (middle) and DR100 (bottom).

4.3 Echocardiography

4.3.1 Standard echocardiography

The present study was aimed to evaluate cardiac function using the echocardiographic techniques after the animals were treated with amiodarone and dronedarone. The standard echocardiographic parameters are consisted of EF, FS, PEP/ET ratio, IVCT, IVRT and Tei index. In this study, EF and FS in every period of amiodarone treated group did not reach statistical significance. While results in the dronedarone treated group, EF and FS were no significant differences in any periods of the treatments (table 5). However EF and FS at the low dose of the dronedarone treated group were lower than the amiodarone treated group (p=0.017 and 0.0176, respectively). The rest of cardiac contractility parameters of amiodarone and dronedarone treated groups from standard echocardiography in the present study; PEP/ET ratio, IVCT, IVRT and Tei index had remained unchanged in every period as shown in table 5.

Table 5 Standard echocardiographic parameters of amiodarone (n=8) and dronedarone (n=8) treatments in anesthetized rabbits.

Index	References	Mean±SEM					
		AM baseline	AM 50	AM100	DR baseline	DR 50	DR100
EF (%)	49.07 – 72.00*	71.22 ±2.92	71.52[1] ±1.23	67.43 ±2.45	63.57 ±2.57	63.82[2] ±2.57	64.17 ±2.69
FS (%)	22.60 – 36.83*	36.89 ±2.09	37.43[1] ±1.03	34.64 ±1.80	31.75 ±1.68	31.86[2] ±1.80	32.20 ±1.82
PEP/ET	<0.4*	0.21 ±0.01	0.19 ±0.01	0.19 ±0.01	0.22 ±0.01	0.18 ±0.02	0.19 ±0.01
IVCT (ms)	52.00** ±3.68	50.50 ±2.41	49.13 ±2.03	47.88 ±3.14	52.13 ±2.86	49.13 ±2.91	46.25 ±1.92
IVRT (ms)	51.42** ±6.19	53.75 ±3.13	54.75 ±3.22	54.50 ±1.78	52.25 ±2.08	54.38 ±2.38	54.63 ±2.89
Tei index	0.60** ±0.20	0.83 ±0.03	0.75 ±0.02	0.81 ±0.07	0.79 ±0.03	0.75 ±0.04	0.73 ±0.02

Different numbers ([1,2]) represent significant differences ($p<0.05$) of the same period between amiodarone and dronedarone treatments; EF = ejection fraction, FS = fractional shortening, PEP = pre-ejection period, ET= ejection time, IVCT = isovolumic contraction time and IVRT = isovolumic relaxation time, *(Fontes-Sousa et al., 2006), **(Fontes-Sousa et al., 2009)

4.2.2 Speckle tracking echocardiography

STE parameters of the LV represent the global heart function. Fractional area change (FAC%) values of either amiodarone and drondarone treatments were no significant difference in any period of treatments (table 6). Time-to-peak standard deviation (TPSD) of global speed and displacement did not reach any statistical significance in any period of treatments. However, TPSD displacement of low dose of the amiodarone treatment group had significant longer interval than dronedarone treated group (table 6).

Table 6 Global parameter values of STE in anesthetized rabbits treated with amiodarone (n=8) or dronedarone (n=8).

Index	Mean±SEM					
	AM baseline	AM 50	AM100	DR baseline	DR 50	DR100
FAC %	25.27 ±1.48	22.80 ±1.42	24.16 ±1.39	23.15 ±1.51	22.98 ±1.31	24.73 ±1.14
Speed_TPSD (ms)	35.61 ±4.89	35.65 ±4.67	34.10 ±2.71	29.79 ±2.12	32.72 ±2.27	29.97 ±3.41
Displace_TPSD (ms)	25.76 ±3.47	26.99 [1] ±2.21	25.03 ±1.82	17.31 ±3.53	18.88 [2] ±2.06	22.00 ±3.39

Different numbers ([1,2]) represent significant differences ($p<0.05$) of the same period between amiodarone and dronedarone treatments.; FAC = fractional area change, Speed_TPSD = time to peak standard deviation of global speed, Displace_TPSD = time to peak standard deviation global displacement.

The present study found that Global radial plane strain at the basal segmental level (GRPS_PSAXB), at the middle segmental level (GRPS_PSAXM), at the apical segmental level (GRPS_PSAXAP), and averaging were not difference among periods of amiodarone and dronedarone. There were also no significant differences in the same treatment periods between both drugs (table 7). Consequently, the GRPS averaging (GRPS_Avg) in either amiodarone or dronedarone treatments were comparable in all treatment periods with no difference within their treatment groups (table 7).

Global circumferential plane strain at basal (GCPS_PSAXB), middle (GCPS_PSAXM), and apical segmental level (GCPS_PSAXAP) values did not achieve statistical difference in any period of amiodarone or dronedarone treated groups. The averaging of circumferential strain (GCPS_Avg) values in all periods of amiodarone and dronedarone treated group had no significant difference both among periods of the same treatment and between drug treatments (table7).

Global radial plane strain rate at basal (GRPSR_PSAXB), middle (GRPSR_PSAXM), and apical segmental level (GRPSR_PSAXAP) values did not achieve any statistical significance in any treatment period of amiodarone and dronedarone treated groups. Similarly, the global radial plane strain rate averaging (GRPSR_Avg) values were also unchanged in all periods of amiodarone and dronedarone treatments (table 8).

Additionally the global circumferential plane strain rate at basal segmental level (GCPRS_PSAXB) value at AM50 was significantly lower than that of the baseline (p=0.045) (table 8). While the difference between the baseline and AM100 values showed only trend of decreasing (p=0.051). GCPRS_PSAXB values of AM50 and AM100 were not significantly different. GCPRS_PSAXB values of dronedarone treatment group were not significantly different in any period. Comparing between treatments, GCPRS_PSAXB values were not statistically different in any period. The global circumferential plane strain rate at middle segmental level (GCRSR_PSAXM), apical segmental level (GCRSR_PSAXAP), and averaging (GCPSR_Avg) were unchanged within group of both amiodarone and dronedarone treatments. Comparison between

drugs at the same treatment periods, these values also did not show statistical significance (table 8).

Nevertheless, time-to-peak standard deviation (TPSD) that represents the cardiac synchrony had no significantly difference in this study neither within group nor between drugs at the same periods, including GRPS_TPSD, GCPS_TPSD, GRPSR_TPSD and GCPSR_TPSD (table 7 and 8).

Table 7 Speckle tracking echocardiography of radial and circumferential strains in anesthetized rabbits treated with amiodarone (n=8) or dronedarone (n=8)

Index	Mean±SEM					
	AM baseline	AM 50	AM100	DR baseline	DR 50	DR100
GPRS_PSAXB (%)	4.27 ±0.76	4.40 ±1.36	2.69 ±0.90	4.24 ±0.89	3.73 ±0.79	4.16 ±0.91
GRPS_PSAXM (%)	11.19 ±1.45	9.89 ±1.36	10.99 ±1.49	11.93 ±2.38	11.22 ±2.25	12.60 ±2.62
GRPS_PSAXAP (%)	11.22 ±2.58	9.39 ±1.97	11.07 ±2.19	12.79 ±1.56	11.89 ±2.48	13.53 ±1.19
GRPS_Avg (%)	8.89 ±1.07	9.15 ±2.08	8.25 ±1.26	9.65 ±1.20	8.86 ±1.11	10.75 ±1.05
GRPS_TPSD (ms)	53.21 ±3.46	54.42 ±4.09	52.07 ±7.04	45.53 ±5.27	50.44 ±1.92	50.57 ±3.78
GCPS_PSAXB (%)	-12.87 ±0.69	-11.62 ±1.31	-13.28 ±0.71	-11.94 ±1.03	-11.62 ±1.06	-11.84 ±0.79
GCPS_PSAXM (%)	-11.62 ±0.91	-11.36 ±1.14	-11.06 ±0.92	-11.15 ±0.68	-11.25 ±0.79	-11.01 ±0.58
GCPS_PSAXAP (%)	-11.82 ±0.87	-9.72 ±0.594=	-9.32 ±1.01	-9.66 ±0.79	-8.98 ±0.54	-10.53 ±0.99
GCPS_Avg (%)	-12.10 ±0.65	-10.89 ±0.84	-11.22 ±0.61	-10.92 ±0.61	-10.62 ±0.59	-8.19 ±2.85
GCPS_TPSD (ms)	19.87 ±4.05	23.81 ±3.53	22.18 ±2.69	20.16 ±2.99	19.25 ±3.93	18.35 ±3.27

Abbreviations; GRPS_PSAXB = global radial plane strain parasternal short axis at basal segmental level, GRPS_PSAXM = global radial plane strain parasternal short axis at middle segmental level, GRPS_PSAXAP = Global radial plane strain parasternal short axis at apical segmental level, GRPS_Avg = global radial plane strain averaging, GRPS_TPSD = time to peak standard deviation of radial strain, GCPS_PSAXB = global circumferential plane strain parasternal short axis at basal segmental level, GCPS_PSAXM = global circumferential plane strain parasternal short axis at middle segmental level, GCPS_PSAXAP = global circumferential plane strain parasternal short axis at apical segmental level, GCPS_Avg = global circumferential plane strain averaging, GCPS_TPSD = time to peak standard deviation of circumferential strain.

Table 8 Speckle tracking echocardiography of radial and circumferential strain rates in anesthetized rabbits treated with amiodarone (n=8) or dronedarone (n=8)

Index	Mean±SEM					
	AM baseline	AM 50	AM100	DR baseline	DR 50	DR100
GRPSR_PSAXB (1/s)	2.19 ±0.25	2.15 ±0.43	2.66 ±0.72	2.86 ±0.34	1.93 ±0.28	2.07 ±0.23
GRPSR_PSAXM (1/s)	2.81 ±0.31	2.67 ±0.45	2.78 ±0.25	2.77 ±0.16	2.39 ±0.29	2.73 ±0.36
GRPSR_PSAXAP (1/s)	2.84 ±0.36	3.59 ±0.86	2.54 ±0.31	2.52 ±0.29	2.52 ±0.26	2.64 ±0.23
GRPSR_Avg (1/s)	2.62 ±0.14	3.18 ±0.49	2.66 ±0.37	2.72 ±0.15	2.28 ±0.16	2.51 ±0.19
GRPSR_TPSD (ms)	36.36 ±3.61	37.69 ±5.74	35.99 ±2.95	35.95 ±3.99	38.25 ±4.16	39.48 ±3.12
GCPSR_PSAXB (1/s)	0.431^{a} ±0.057	0.204^{b} ±0.076	$0.251^{a,b}$ ±0.071	0.224 ±0.094	0.311 ±0.041	0.234 ±0.058
GCPSR_PSAXM (1/s)	0.329 ±0.073	0.351 ±0.049	0.134 ±0.038	0.249 ±0.083	0.215 ±0.046	0.278 ±0.041
GCPSR_PSAXAP (1/s)	0.515 ±0.204	0.485 ±0.113	0.294 ±0.073	0.279 ±0.057	0.290 ±0.064	0.291 ±0.062
GCPSR_Avg (1/s)	0.425 ±0.096	0.347 ±0.035	0.228 ±0.046	0.250 ±0.037	0.271 ±0.031	0.246 ±0.045
GCPSR _TPSD (ms)	52.14 ±6.92	61.53 ±4.35	56.61 ±6.14	57.82 ±4.14	58.98 ±2.47	59.39 ±5.88

Different letters (^{a,b}) within the same drug treatments represent significant differences ($p<0.05$); GRPSR_PSAXB = global radial plane strain rate parasternal short axis at basal segmental level, GRPSR_PSAXM = global radial plane strain rate parasternal short axis at middle segmental level, GRPSR_PSAXAP = global radial plane strain rate parasternal short axis at apical segmental level, GRPSR_Avg = global radial plane strain rate averaging, GRPSR_TPSD = time to peak standard deviation of radial strain rate, GCPSR_PSAXB = global circumferential plane strain rate parasternal short axis at basal segmental level, GCPSR_PSAXM = global circumferential plane strain rate parasternal short axis at middle segmental level, GCPSR_PSAXAP = global circumferential plane strain rate parasternal short axis at apical segmental level, GCPSR_Avg = global circumferential plane strain rate averaging, GCPSR_TPSD = time to peak standard deviation of circumferential strain rate

CHAPTER V
DISCUSSIONS

5.1 General condition

5.1.1 Complete blood count monitoring

In the present study we had collected blood samples for complete blood count analysis to validate whether amiodarone or dronedarone have any effects on the hemopoeitic system. Since amiodarone has been available more than 40 years, there were several medical reports showed that amiodarone would induce pancytopenia and bone marrow granuloma in chronic amiodarone treated patients (Boutros et al., 2000; Yamreudeewong et al., 2000; Moran and Manoharan, 2002; Mukhopadhyay et al., 2004; Bilello et al., 2006; Erie et al., 2010). Moreover, the previous reports showed that after the therapy was stopped, the granuloma and pancytopenia were gradually improved (Boutros et al., 2000; Yamreudeewong et al., 2000; Moran and Manoharan, 2002; Mukhopadhyay et al., 2004; Bilello et al., 2006; Erie et al., 2010). Our study has also been showed decreasing trend of white blood cells, red blood cells and platelets in amiodarone treatment. However, there was no significant difference between the baseline and amiodarone-treated groups. Due to the major in time-dependent, 2 weeks treatment of the present study was shorter than clinical cases reported in humans, which usually more than 3 months or up to 2 years of treatment. Moreover, the newer drug, dronedarone has not been reported its toxicity on the hemopoietic system. Surprisingly, the present study has shown significantly reduction of red blood cells in dronedarone treated groups compared to the baseline. Nevertheless, the value was still in the normal limit. This could be due to hydration status or blood collection that may affect to the results.

5.1.2 Blood chemistry monitoring

Blood chemistry analysis in the present study has been provided information for hepatic and renal profiles. These organs are major targets on drug metabolism, clearance, and drug toxicity, especially in chronic treatment (Lewis et al., 1989; Felser et al., 2013). Hepatotoxicity is one of major adverse effects in amiodarone and dronedarone treated patients. The toxicity was dose-dependent inhibition of mitochondrial respiratory beta-oxidation in rat and mouse isolated hepatic cells (Waldhauser et al., 2006; Felser et al., 2014). There were many medical records reported hepatotoxicity of these antiarrhythmic agents from asymtomatic elevation of serum aminotransferase levels to symptomatic hepatitis in patients who received amiodarone for longer than 2 weeks or months (Lewis et al., 1989; Ratz Bravo et al., 2005) and also in patients who received dronedarone(Jahn et al., 2013). However this adverse effect could be reversible after dose decreasing or stop taking these agents (Lewis et al., 1989). The present study demonstrated that rabbit hepatic enzymes, both AST and ALT seemed to be decreased in both treatment groups, but there were still in the normal range. The decreasing of these aminotransferase enzymes would be impacted by aging (Goh et al., 2015). Moreover, ALP was raised in only the high dosage of amiodarone, but it also was in the normal limit. Beside, ALP levels could be higher 2-3 times in young animals. This enzyme can be found in the heart, kidneys, intestine or pancreas. Therefore, the elevation of this non specific marker, ALP, should be interpreted with caution. Thus the 50 and 100 mg/kg/day doses of amiodarone and dronedarone treatments in the present study could not produce the hepatotoxic effect on rabbits in 2 weeks of the study.

Kidneys are the main organ for elimination of these drugs. Conti and colleagues reported incidences and pointed association of dronedarone and amiodarone treatment with acute renal failure in Italian database (Conti et al., 2015). Dronedarone could cause serum Cr increasing due to partially inhibition of the organic cation transporter system in nephrons (Tschuppert et al., 2007), and it could cause acute renal failure within first 13 days of treatment in elderly patients (Biagi et al., 2013). In the present study, BUN and Cr have been remained the same compared

to the baselines in both amiodarone and dronedarone treated groups, and there were still in the normal range. It could possibly due to either time- or dose-dependent, but we could not demonstrate the renal dysfunction in rabbits within two weeks of the present study. Nevertheless, patients with cardiovascular diseases would take several medicines which can result in combined adverse drug reaction. There were several studies reported about drug combination reaction caused rhabdomyolysis between simvastatin and amiodarone, which simvastatin is metabolized by CYP3A4 and amiodarone is a CYP3A4 inhibitor (Roten et al., 2004; Schmidt et al., 2007; Pietsch et al., 2016). The reaction could lead to secondary acute renal failure. However, discontinuation of the combination treatment with or without dialysis could reverse this adverse effect (Schmidt et al., 2007).

5.1.3 Thyroid hormone monitoring

Another side effect of amiodarone is thyroid dysfunction. Most patients who received amiodarone for a long term may remain euthyroid. Amiodarone could induce either hypothyroidism or thyrotoxicosis. Many studies found that long-term amiodarone treatment decreased serum T_4 levels or AIH (Martino et al., 2001). On the other hand, some studies found that amiodarone can increase serum T_4 level or AIT which depends on an individual iodine status of subjects (Martino et al., 2001; Hofmann et al., 2008; Padmanabhan, 2010). There were two types of amiodarone-induced thyrotoxicosis; type 1 which is occurred by excess iodine-induced thyroid hormone synthesis and type 2 which may have normal thyroid glands but amiodarone itself causes destructive thyroiditis (Padmanabhan, 2010). The present study has found that 2-weeks of amiodarone treatment cause an increase in serum total T_4 in rabbits. It could be that in early phase of amiodarone treatment, serum total T_4 might be high and would decrease afterward (Wiersinga, 1997). In rats, the destructive thyroiditis (type II) was also reported (Pitsiavas et al., 1997) with evidence of cells apoptosis and necrosis via an iodine-independent mechanism (Burikhanov and Matsuzaki, 2000; Di Matola et al., 2000). Nevertheless, AIT is preferential in

iodine-deficient areas especially in males (Eskes and Wiersinga, 2009). Therefore, all rabbits in the present study were male which leaded to risks of AIT.

On the other hand, dronedarone is a deiodenated form, and reported lesser side effects than amiodarone. There were many researches showed that dronedarone was not induce abnormal thyroid hormone levels (Pantos et al., 2002; Pantos et al., 2005; Patel et al., 2009), whereas there were a few reports found that it could cause thyroid dysfunction in rats (Chatelain et al., 1995; Van Beeren et al., 2003; Jiang et al., 2016). Van Beeren and co-workers showed that dronedarone decreased total and free forms of T_3 and T_4 levels in vivo mainly via its active metabolites, and dronedarone also tended to decrease plasma TSH (Van Beeren et al., 2003). Moreover, dronedarone might cause thyroid cells damage in early stage and degeneration afterward, resulted in a decrease of T_4 level after the chronic treatment (Jiang et al., 2016). Our results showed a decrease of serum total T_4 after dronedarone treatments. Since our data have suggested that dronedarone may produce adverse effect on thyroid glands in male rabbits. The monitoring of adverse effect in humans should be concerned.

5.2 Heart rate and Heart rate variability

5.2.1 Heart rate

The heart possesses the automaticity due to pace maker cells in the sinoatrial node, which creates spontaneous depolarization. The mechanism depends on I_{Ca}, I_f, and I_K currents. Amiodarone and dronedarone are multi-ion channel blockers which have targets on the heart for curing arrhythmias. The previous study showed that anesthetized dogs were decreased heart rate significantly after intravenous injection of amiodarone which affected to both atria and ventricular rates (Platou and Refsum, 1986). This effect was also found in conscious rats (Dias da Silva et al., 2002b) and humans (Figa et al., 1994). Moreover, dronedarone was reported bradycardia in rats (Chatelain et al., 1995; Salgado et al., 2007), pigs (Sobrado et al., 2013), dogs (Saengklub et al., 2016a; Saengklub et al., 2016b), and humans (Levine et al., 2010). In the present study, the negative chronotropic effect

was created by both amiodarone and dronedarone in conscious rabbits. These effects were enhanced after increasing the dose. This negative chronotropy may be due to the effect of multichannel blocking properties and beta-adrenergic blocking activity of these drugs (Altomare et al., 2000; Gautier et al., 2003; Kathofer et al., 2005). Chronic treatments of these agents can also down regulate the beta-adrenoceptor (Chatelain et al., 1995), causing lower calcium entrances to myocardium by inhibition of Gs proteins. Amiodarone and dronedarone markedly prolonged APD90, ERP, and RR interval in isolated rabbit myocadial cells (Sun et al., 2002) leading to slow the heart rate.

5.2.2 Frequency domain of HRV

Generally, heart rate is influenced by the ANS, which plays roles on the top of intrinsic heart rate via adrenergic and/or muscarinic stimulation. In healthy subjects, heart rhythm is fluctuation because of sympatovagal balance, and causes the duration changes from beat to beat. HRV is broadly used to monitor cardiac function during the past few decades. The concept of the analysis is to measure heart rate and to study beat-to-beat behavior influenced by the sympatovagal control. It could predict mortality risk in patients with cardiovascular and non-cardiovascular diseases (Vanderlei et al., 2009). The clinical studies have shown HRV decreasing related to adverse events and higher risk of mortality (Winchell and Hoyt, 1996; Vanderlei et al., 2009). There are two useful indices for linear analysis of HRV, which is the time domain and the frequency domain. Heart rate variability has been analyzed in the short term as frequency domain by spectral analysis technique. This technique has been confirmed to be a suitable pre-diagnostic tool for screening heart function that have sensitivities more than 72% and a specificity of 100% for distinguishability between healthy and heart disease subjects (Heitmann et al., 2011).

In the present study, we had performed the short term analysis of HRV in rabbits. We found that total power spectrum was decreased in both amiodarone and dronedarone treated groups, mainly due to the decrease of LF components in the dose-dependent manner. This might partially be due to beta adrenergic inhibition of

amiodarone and dronedarone, leading to sympathetic suppression (Chatelain et al., 1995). Similarly to rats, amiodarone increased vagal activity and decreased sympathetic activity, causing significant lowering of the low frequency component (Dias Da Silva et al., 2002a; Dias da Silva et al., 2002b). Also, breathing variability may involve in decreasing of the LF component (Beda et al., 2014). Nevertheless, the regulation of the LF component is still unclear.

On the other hand, we had not found increasing of the HF component in both amiodarone-treated group and dronedarone-treated group. In general, the HF band represents to parasympathetic regulation (Berntson et al., 1997). These may be suggested that these drugs might not affect directly to the parasympathetic system of the rabbits. Theoretically, the parasympathetic activity may be enhanced because of sympathetic activity suppression by these drugs. Additionally, the LF/HF ratio was also reduced in both treatment groups. These results may be related to a decrease of the LF component, but unchanging of the HF component. Lastly, the VLF component was unchanged in both treatment groups and every period of time. Normally the very low frequency component is associated with thermoregulation and plasma renin activity (Task-Force., 1996; Berntson et al., 1997), which amiodarone and dronedarone have not involved with these systems.

5.3 Echocardiographic assessments

In the present study, we had performed standard and STE methods to determine cardiac contractility related to the antiarrhythmic drugs, amiodarone and dronedarone, in rabbits. We found that cardiac contractility remained unchanged in anesthetized rabbits between baselines and drug-treated groups when performed with standard echocardiography. Besides, EF and FS of the DR50 were lower than the same dosage period of amiodarone treatment, although there were not considered changing from their baselines. The previous study has shown that dronedarone reduce heart rate without affecting to cardiac contractility in anesthetized pigs (Sobrado et al., 2013). Moreover, the short-term oral dronedarone treatment had no effect on cardiac inotropy and dromotropy in conscious dogs (Saengklub et al.,

2016b). On the other hand, the acute effect of intravenous dronedarone could have negative inotropic effect in anesthetized dogs (Saengklub et al., 2016a). The US Food and Drug Administration approval data show that oral amiodarone treatment does not have any significant changes of the LVEF, even in patients with depressed EF, while acute intravenous administration of amiodarone might have a mild negative inotropic effect in humans (Zipes et al., 1984). In normal dog hearts, amiodarone did not show any effects on +dP/dt max, although it reduced +dP/dt max markedly in infracted hearts (Ware et al., 1991). Amiodarone was also reported that it might cause hypotension, negative chronotropy, negative inotropy and negative lusitropy, which demonstrated by decreases in +dP/dt max and -dP/dt min in conscious rats (Salgado et al., 2007).

Many studies have been investigated and compared sensitivity between standard echocardiography and STE. The results gave credit to STE that was more sensitive for early detection in various cardiac diseases (Dandel and Hetzer, 2009; Li et al., 2014; Du et al., 2015), and the detection covers most of LV segments; basal, middle and apical parts. While STE parameters in the present study mostly were unchanged from the baselines in both treatment groups, except the GCPSR at the basal level which was lower when treated with amiodarone. A previous study reported that amiodarone and dronedarone could alter cardiac contractility by decreasing left ventricular dP/dtmax in isolated ventricular myocytes of guinea pigs (Gautier et al., 2003), which the negative inotropy caused by effects of class II and IV antiarrhythmic properties of both agents that block beta-adrenergic receptors and calcium channels, respectively. Although there was a contrast in the present study which only found changing in a variable of the amiodarone group, but not the dronedarone group. It may by cause by differently in total summation of actions in the whole rabbit heart in the present study. Moreover, several previous studies have shown that there were no significant differences between standard echocardiography and STE methods in healthy subjects (Schwarzwald et al., 2009; Decloedt et al., 2011; Decloedt et al., 2013; Berli et al., 2015), whereas chronic amiodarone treatment can down regulate the beta-adrenoceptors (Chatelain et al., 1995), causing negative

chronotropy and leading to detection in STE. In the present study, we found that STE may not have higher sensitivity than the standard echocardiography when performing in the amiodarone and dronedarone treated rabbits.. This may suggested that the use of STE to monitor cardiac performance in rabbits may need further investigations.

5.4 Future study and limitations

In vivo experiment has limitation for the cardiac contractility measurement due to uncontrolled preload and afterload that would play role on the LV function in this model. Therefore, to avoid these effects, cardiac contractility can be confirmed by using the isolated heart or the isolate myofibril in the future. Moreover, the rabbit has a large sternum but a small left cardiac notch; therefore, the left parasternal longitudinal plane of the heart could not be performed in this study. This may reduce the sensitivity of speckle tracking echocardiography because the longitudinal plane provides better muscle moving directions that away or toward the ultrasound probe compared to the short axis from the right parasternal view that we did in the present study.

In the future, histopathologic studies of thyroid glands will provide more details on the development of amiodarone induced thyrotoxicosis and dronedarone induced hypothyroidism in a rabbit model.

CHAPTER VI
CONCLUSION

Oral treatments of amiodarone and dronedarone in rabbits for 2 weeks have not clinically altered CBC and blood chemistry. There is a markedly bradycardia effect of both drugs. HRV in the rabbits is decreased due to a decrease of the LF component suggesting that it may have an inhibition of beta-adrenergic receptors in the heart, leading to sympathetic suppression. The standard echocardiography and STE were comparable on cardiac function assessment, although STE may provide further information in addition to standard echocardiography. In the present study, we also demonstrate that amiodarone may produce negative inotropic effect more than dronedarone showed by lowering of GCPRS at LV basal level. Moreover, amiodarone may induce thyrotoxicosis while dronedarone cause hypothyroidism in a rabbit model.

REFERENCES

Altomare C, Barbuti A, Viscomi C, Baruscotti M and DiFrancesco D 2000. Effects of dronedarone on acetylcholine-activated current in rabbit SAN cells. Br J Pharmacol. 130(6): 1315-1320.

Andreasen F, Agerbaek H, Bjerregaard P and Gotzsche H 1981. Pharmacokinetics of amiodarone after intravenous and oral administration. Eur J Clin Pharmacol. 19(4): 293-299.

Bassani JW, Bassani RA and Bers DM 1994. Relaxation in rabbit and rat cardiac cells: species-dependent differences in cellular mechanisms. J Physiol. 476(2): 279-293.

Beda A, Simpson DM, Carvalho NC and Carvalho AR 2014. Low-frequency heart rate variability is related to the breath-to-breath variability in the respiratory pattern. Psychophysiology. 51(2): 197-205.

Berli AS, Jud Schefer R, Steininger K and Schwarzwald CC 2015. The use of strain, strain rate, and displacement by 2D speckle tracking for assessment of systolic left ventricular function in goats: applicability and influence of general anesthesia. Cardiovasc Ultrasound. 13: 11.

Berntson GG, Bigger JT, Jr., Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH and van der Molen MW 1997. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. 34(6): 623-648.

Biagi C, Venegoni M, Melis M, Buccellato E, Montanaro N and Motola D 2013. Dronedarone-associated acute renal failure: evidence coming from the Italian spontaneous ADR reporting database. Br J Clin Pharmacol. 75(5): 1351-1355.

Bilello SJ, Bao F, Veillon DM, Muldoon R and Cotelingam JD 2006. Pathology case of the month. Elderly man with pancytopenia. Bone marrow granulomas secondary to amiodarone. J La State Med Soc. 158(1): 10-12.

Bosch RF, Li GR, Gaspo R and Nattel S 1999. Electrophysiologic effects of chronic amiodarone therapy and hypothyroidism, alone and in combination, on guinea pig ventricular myocytes. J Pharmacol Exp Ther. 289(1): 156-165.

Boutros NY, Dilly S and Bevan DH 2000. Amiodarone-induced bone marrow granulomas. Clin Lab Haematol. 22(3): 167-170.

Burashnikov A, Belardinelli L and Antzelevitch C 2010. Acute dronedarone is inferior to amiodarone in terminating and preventing atrial fibrillation in canine atria. Heart Rhythm. 7(9): 1273-1279.

Burikhanov RB and Matsuzaki S 2000. Excess iodine induces apoptosis in the thyroid of goitrogen-pretreated rats in vivo. Thyroid. 10(2): 123-129.

Chatelain P, Meysmans L, Matteazzi JR, Beaufort P and Clinet M 1995. Interaction of the antiarrhythmic agents SR 33589 and amiodarone with the beta-adrenoceptor and adenylate cyclase in rat heart. Br J Pharmacol. 116(3): 1949-1956.

Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH and Investigators P 2011. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 365(24): 2268-2276.

Conti V, Biagi C, Melis M, Fortino I, Donati M, Vaccheri A, Venegoni M and Motola D 2015. Acute renal failure in patients treated with dronedarone or amiodarone: a large population-based cohort study in Italy. Eur J Clin Pharmacol. 71(9): 1147-1153.

Dandel M and Hetzer R 2009. Echocardiographic strain and strain rate imaging--clinical applications. Int J Cardiol. 132(1): 11-24.

Decloedt A, Verheyen T, Sys S, De Clercq D and van Loon G 2011. Quantification of left ventricular longitudinal strain, strain rate, velocity, and displacement in healthy horses by 2-dimensional speckle tracking. J Vet Intern Med. 25(2): 330-338.

Decloedt A, Verheyen T, Sys S, De Clercq D and van Loon G 2013. Two-dimensional speckle tracking for quantification of left ventricular circumferential and radial wall motion in horses. Equine Vet J. 45(1): 47-55.

Di Matola T, D'Ascoli F, Fenzi G, Rossi G, Martino E, Bogazzi F and Vitale M 2000. Amiodarone induces cytochrome c release and apoptosis through an iodine-independent mechanism. J Clin Endocrinol Metab. 85(11): 4323-4330.

Dias Da Silva VJ, Gnecchi-Ruscone T, Lavelli B, Bellina V, Manzella D, Porta A, Malliani A and Montano N 2002a. Opposite effects of iv amiodarone on cardiovascular vagal and sympathetic efferent activities in rats. Am J Physiol Regul Integr Comp Physiol. 283(2): R543-548.

Dias da Silva VJ, Viana Publio CC, de Melo Alves R, Fazan R, Jr., Ruscone TG, Porta A, Malliani A, Salgado HC and Montano N 2002b. Intravenous amiodarone modifies autonomic balance and increases baroreflex sensitivity in conscious rats. Auton Neurosci. 95(1-2): 88-96.

Djandjighian L, Planchenault J, Finance O, Pastor G, Gautier P and Nisato D 2000. Hemodynamic and antiadrenergic effects of dronedarone and amiodarone in animals with a healed myocardial infarction. J Cardiovasc Pharmacol. 36(3): 376-383.

Du WH, Wang X, Xiong XQ, Li T and Liang HP 2015. Role of speckle tracking imaging in the assessment of myocardial regional ventricular function in experimental blunt cardiac injury. Chin J Traumatol. 18(4): 223-228.

Erie AJ, McClure RF and Wolanskyj AP 2010. Amiodarone-induced bone marrow granulomas: an unusual cause of reversible pancytopenia. Hematol Rep. 2(1): e6.

Eskes SA and Wiersinga WM 2009. Amiodarone and thyroid. Best Pract Res Clin Endocrinol Metab. 23(6): 735-751.

Everts ME, Verhoeven FA, Bezstarosti K, Moerings EP, Hennemann G, Visser TJ and Lamers JM 1996. Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology. 137(10): 4235-4242.

Felser A, Blum K, Lindinger PW, Bouitbir J and Krahenbuhl S 2013. Mechanisms of hepatocellular toxicity associated with dronedarone--a comparison to amiodarone. Toxicol Sci. 131(2): 480-490.

Felser A, Stoller A, Morand R, Schnell D, Donzelli M, Terracciano L, Bouitbir J and Krahenbuhl S 2014. Hepatic toxicity of dronedarone in mice: role of mitochondrial beta-oxidation. Toxicology. 323: 1-9.

Figa FH, Gow RM, Hamilton RM and Freedom RM 1994. Clinical efficacy and safety of intravenous Amiodarone in infants and children. Am J Cardiol. 74(6): 573-577.

Finance O, Manning A and Chatelain P 1995. Effects of a new amiodarone-like agent, SR 33589, in comparison to amiodarone, D,L-sotalol, and lignocaine, on ischemia-induced ventricular arrhythmias in anesthetized pigs. J Cardiovasc Pharmacol. 26(4): 570-576.

Fontes-Sousa AP, Bras-Silva C, Moura C, Areias JC and Leite-Moreira AF 2006. M-mode and Doppler echocardiographic reference values for male New Zealand white rabbits. Am J Vet Res. 67(10): 1725-1729.

Fontes-Sousa AP, Moura C, Carneiro CS, Teixeira-Pinto A, Areias JC and Leite-Moreira AF 2009. Echocardiographic evaluation including tissue Doppler imaging in New Zealand white rabbits sedated with ketamine and midazolam. Vet J. 181(3): 326-331.

Frey B, Heger G, Mayer C, Kiegler B, Stohr H and Steurer G 1996. Heart rate variability in isolated rabbit hearts. Pacing Clin Electrophysiol. 19(11 Pt 2): 1882-1885.

García-González MA, Fernández-Chimeno M, Ferrer J, Escorihuela RM, Parrado E, Capdevila L, Benítez A, Angulo R, Rodríguez FA, Iglesias X, Bescós R, Marina M, Padullés JM and Ramos-Castro J 2010. New indices for quantification of the power spectrum of heart rate variability time series without the need of any frequency band definition. Physiol Meas. 32; 995–1009.

Gautier P, Guillemare E, Marion A, Bertrand JP, Tourneur Y and Nisato D 2003. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. J Cardiovasc Pharmacol. 41(2): 191-202.

Gill J, Hell R and AFitton A 1992. Amiodarone An Overview of its Pharmacological Properties, and Review of its therapeutic use in cardiac arrhythmia. Drugs. 43: 69-110.

Goh GBB, Pagadala MR, Dasarathy J, Unalp-Arida A, Pai RK, Yerian L, Khiyami A, Sourianarayanane A, Sargent R, Hawkins C, Dasarathy S and McCullough AJ 2015. Age Impacts Ability of Aspartate-Alanine Aminotransferase Ratio to Predict Advanced Fibrosis in Nonalcoholic Fatty Liver Disease. Dig Dis Sci. 60(6): 1825-1831.

Guillemare E, Marion A, Nisato D and Gautier P 2000. Inhibitory effects of dronedarone on muscarinic K+ current in guinea pig atrial cells. J Cardiovasc Pharmacol. 36(6): 802-805.

Harjai KJ and Licata AA 1997. Effects of amiodarone on thyroid function. Ann Intern Med. 126(1): 63-73.

Harris L, McKenna WJ, Rowland E, Holt DW, Storey GC and Krikler DM 1983. Side effects of long-term amiodarone therapy. Circulation. 67(1): 45-51.

Heitmann A, Huebner T, Schroeder R, Perz S and Voss A 2011. Multivariate short-term heart rate variability: a pre-diagnostic tool for screening heart disease. Med Biol Eng Comput. 49(1): 41-50.

Hodeige D, Heyndrickx JP, Chatelain P and Manning A 1995. SR 33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anaesthetized and conscious dogs. Eur J Pharmacol. 279(1): 25-32.

Hofmann A, Nawara C, Ofluoglu S, Holzmannhofer J, Strohmer B and Pirich C 2008. Incidence and predictability of amiodarone-induced thyrotoxicosis and hypothyroidism. Wien Klin Wochenschr. 120(15-16): 493-498.

Hoy SM and Keam SJ 2009. Dronedarone. Drugs. 69(12): 1647-1663.

Huemer M, Sarganas G, Bronder E, Klimpel A, Garbe E and Haverkamp W 2015. Torsade de pointes tachycardia in a patient on dronedarone therapy. Pharmacotherapy. 35(5): e61-65.

Jahn S, Zollner G, Lackner C and Stauber RE 2013. Severe toxic hepatitis associated with dronedarone. Curr Drug Saf. 8(3): 201-202.

James J, Martin L, Krenz M, Quatman C, Jones F, Klevitsky R, Gulick J and Robbins J 2005. Forced expression of alpha-myosin heavy chain in the rabbit ventricle results in cardioprotection under cardiomyopathic conditions. Circulation. 111(18): 2339-2346.

Jiang LQ, Chen SJ, Xu JJ, Ran Z, Ying W and Zhao SG 2016. Dronedarone and Amiodarone Induce Dyslipidemia and Thyroid Dysfunction in Rats. Cell Physiol Biochem. 38(6): 2311-2322.

Kathofer S, Thomas D and Karle CA 2005. The novel antiarrhythmic drug dronedarone: comparison with amiodarone. Cardiovasc Drug Rev. 23(3): 217-230.

Klein I and Ojamaa K 2001. Thyroid hormone and the cardiovascular system. N Engl J Med. 344(7): 501-509.

Kodama I, Kamiya K and Toyama J 1997. Cellular electropharmacology of amiodarone. Cardiovasc Res. 35(1): 13-29.

Lalevee N, Nargeot J, Barrere-Lemaire S, Gautier P and Richard S 2003. Effects of amiodarone and dronedarone on voltage-dependent sodium current in human cardiomyocytes. J Cardiovasc Electrophysiol. 14(8): 885-890.

Latini R, Tognoni G and Kates RE 1984. Clinical pharmacokinetics of amiodarone. Clin Pharmacokinet. 9(2): 136-156.

Levine TB, Giles T, Radzik D and Ghali JK 2010. Effect of dronedarone on exercise capacity and cardiac function in patients with severe left ventricular dysfunction and compensated stable heart failure. Cardiovasc Drugs Ther. 24(5-6): 449-458.

Lewis JH, Ranard RC, Caruso A, Jackson LK, Mullick F, Ishak KG, Seeff LB and Zimmerman HJ 1989. Amiodarone hepatotoxicity: prevalence and clinicopathologic correlations among 104 patients. Hepatology. 9(5): 679-685.

Li T, Liu JJ, Du WH, Wang X, Chen ZQ and Zhang LC 2014. 2D speckle tracking imaging to assess sepsis induced early systolic myocardial dysfunction and its underlying mechanisms. Eur Rev Med Pharmacol Sci. 18(20): 3105-3114.

Magro SA, Lawrence EC, Wheeler SH, Krafchek J, Lin HT and Wyndham CR 1988. Amiodarone pulmonary toxicity: prospective evaluation of serial pulmonary function tests. J Am Coll Cardiol. 12(3): 781-788.

Malik M, Camm AJ, Janse MJ, Julian DG, Frangin GA and Schwartz PJ 2000. Depressed heart rate variability identifies postinfarction patients who might benefit from prophylactic treatment with amiodarone: a substudy of EMIAT (The European Myocardial Infarct Amiodarone Trial). J Am Coll Cardiol. 35(5): 1263-1275.

Malliani A, Pagani M and Lombardi F 1995. Power spectral analysis of heart rate variability and baroreflex gain. Clin Sci (Lond). 89(5): 555-556.

Manning AS, Bruyninckx C, Ramboux J and Chatelain P 1995. SR 33589, a new amiodarone-like agent: effect on ischemia- and reperfusion-induced arrhythmias in anesthetized rats. J Cardiovasc Pharmacol. 26(3): 453-461.

Manzo A, Ootaki Y, Ootaki C, Kamohara K and Fukamachi K 2009. Comparative study of heart rate variability between healthy human subjects and healthy dogs, rabbits and calves. Lab Anim. 43(1): 41-45.

Markou K, Georgopoulos N, Kyriazopoulou V and Vagenakis AG 2001. Iodine-Induced hypothyroidism. Thyroid. 11(5): 501-510.

Martino E, Bartalena L, Bogazzi F and Braverman LE 2001. The effects of amiodarone on the thyroid. Endocr Rev. 22(2): 240-254.

Masi S, de Clety SC, Anslot C and Detaille T 2009. Acute amiodarone toxicity due to an administration error: could excipient be responsible? Br J Clin Pharmacol. 67(6): 691-693.

Miyata S, Minobe W, Bristow MR and Leinwand LA 2000. Myosin heavy chain isoform expression in the failing and nonfailing human heart. Circ Res. 86(4): 386-390.

Moran SK and Manoharan A 2002. Amiodarone-induced bone marrow granulomas. Pathology. 34(3): 267-269.

Mukhopadhyay S, Mukhopadhyay S, Abraham NZ, Jr., Jones LA, Howard L and Gajra A 2004. Unexplained bone marrow granulomas: is amiodarone the culprit? A report of 2 cases. Am J Hematol. 75(2): 110-112.

Naccarelli GV, Wolbrette DL, Levin V, Samii S, Banchs JE, Penny-Peterson E and Gonzalez MD 2011. Safety and efficacy of dronedarone in the treatment of atrial fibrillation/flutter. Clin Med Insights Cardiol. 5: 103-119.

Nattel S and Talajic M 1988. Recent advances in understanding the pharmacology of amiodarone. Drugs. 36(2): 121-131.

Padmanabhan H 2010. Amiodarone and thyroid dysfunction. South Med J. 103(9): 922-930.

Panfilov AV 2006. Is heart size a factor in ventricular fibrillation? Or how close are rabbit and human hearts? Heart Rhythm. 3(7): 862-864.

Pantos C, Mourouzis I, Delbruyere M, Malliopoulou V, Tzeis S, Cokkinos DD, Nikitas N, Carageorgiou H, Varonos D, Cokkinos D and Nisato D 2002. Effects of dronedarone and amiodarone on plasma thyroid hormones and on the basal and postischemic performance of the isolated rat heart. Eur J Pharmacol. 444(3): 191-196.

Pantos C, Mourouzis I, Malliopoulou V, Paizis I, Tzeis S, Moraitis P, Sfakianoudis K, Varonos DD and Cokkinos DV 2005. Dronedarone administration prevents body weight gain and increases tolerance of the heart to ischemic stress: a possible involvement of thyroid hormone receptor alpha1. Thyroid. 15(1): 16-23.

Patel C, Yan GX and Kowey PR 2009. Dronedarone. Circulation. 120(7): 636-644.

Pfeiffer A, Vidon N, Bovet M, Rongier M and Bernier JJ 1990. Intestinal absorption of amiodarone in man. J Clin Pharmacol. 30(7): 615-620.

Piacentino V, 3rd, Weber CR, Chen X, Weisser-Thomas J, Margulies KB, Bers DM and Houser SR 2003. Cellular basis of abnormal calcium transients of failing human ventricular myocytes. Circ Res. 92(6): 651-658.

Pietsch U, Muller-Hocker C and Filipovic M 2016. [Brown urine : Myoglobin-induced renal failure after concomitant administration of simvastatin and amiodarone]. Anaesthesist. 65(5): 366-368.

Pitsiavas V, Smerdely P, Li M and Boyages SC 1997. Amiodarone induces a different pattern of ultrastructural change in the thyroid to iodine excess alone in both the BB/W rat and the Wistar rat. Eur J Endocrinol. 137(1): 89-98.

Platou ES and Refsum H 1986. Acute electrophysiologic and blood pressure effects of amiodarone and its solvent in the dog. Acta Pharmacol Toxicol (Copenh). 58(3): 163-168.

Puglisi JL, Bassani RA, Bassani JW, Amin JN and Bers DM 1996. Temperature and relative contributions of Ca transport systems in cardiac myocyte relaxation. Am J Physiol. 270(5 Pt 2): H1772-1778.

Ratz Bravo AE, Drewe J, Schlienger RG, Krahenbuhl S, Pargger H and Ummenhofer W 2005. Hepatotoxicity during rapid intravenous loading with amiodarone: Description of three cases and review of the literature. Crit Care Med. 33(1): 128-134; discussion 245-126.

Reiser PJ, Portman MA, Ning XH and Schomisch Moravec C 2001. Human cardiac myosin heavy chain isoforms in fetal and failing adult atria and ventricles. Am J Physiol Heart Circ Physiol. 280(4): H1814-1820.

Roden DM 1993. Pharmacokinetics of amiodarone: implications for drug therapy. Am J Cardiol. 72(16): 45F-50F.

Ronzhina M, Janousek O, Scheer P, Novakova M, Provaznik I and Kolarova J 2010. Determination of the frequency bands for heart rate variability: Studies on the intact and isolated rabbit hearts. Comput Cardiol. 37;927–930.

Rosa GM, Bianco D, Parodi A, Valbusa A, Zawaideh C, Bizzarri N, Ferrero S and Brunelli C 2014. Pharmacokinetic and pharmacodynamic profile of dronedarone , a new antiarrhythmic agent for the treatment of atrial fibrillation. Expert Opin Drug Metab Toxicol. 10(12): 1751-1764.

Roten L, Schoenenberger RA, Krahenbuhl S and Schlienger RG 2004. Rhabdomyolysis in association with simvastatin and amiodarone. Ann Pharmacother. 38(6): 978-981.

Saengklub N, Limprasutr V, Sawangkoon S, Buranakarl C, Hamlin RL and Kijtawornrat A 2016a. Acute effects of intravenous dronedarone on electrocardiograms, hemodynamics and cardiac functions in anesthetized dogs. J Vet Med Sci. 78(2): 177-186.

Saengklub N, Youngblood B, Del Rio C, Sawangkoon S, Hamlin RL and Kijtawornrat A 2016b. Short-term effects of oral dronedarone administration on cardiac

function, blood pressure and electrocardiogram in conscious telemetry dogs. J Vet Med Sci. 78(6): 977-985.

Salgado HC, Simoes GM, Santana Filho VJ, Dias da Silva VJ, Salgado MC and Fazan R, Jr. 2007. Negative inotropic and lusitropic effects of intravenous amiodarone in conscious rats. Clin Exp Pharmacol Physiol. 34(9): 870-875.

Sanofi-Aventis 2009. Dronedarone (Multaq) for atrial fibrillation. Med Lett Drugs Ther. 51(1322): 78-80.

Schmidt GA, Hoehns JD, Purcell JL, Friedman RL and Elhawi Y 2007. Severe rhabdomyolysis and acute renal failure secondary to concomitant use of simvastatin, amiodarone, and atazanavir. J Am Board Fam Med. 20(4): 411-416.

Schwarzwald CC, Schober KE, Berli AS and Bonagura JD 2009. Left ventricular radial and circumferential wall motion analysis in horses using strain, strain rate, and displacement by 2D speckle tracking. J Vet Intern Med. 23(4): 890-900.

Shalaby N 2009. Histological Study of the Effect of Amiodarone on Thyroid Follicular Cells in Albino Rat and its Management Using Carbimazole with and without Prednisolone. Egypt. J. Histol. 32: 306-314.

Singh BN 2006. Amiodarone: a multifaceted antiarrhythmic drug. Curr Cardiol Rep. 8(5): 349-355.

Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH, Euridis and Investigators A 2007. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med. 357(10): 987-999.

Sloskey GE 1983. Amiodarone: a unique antiarrhythmic agent. Clin Pharm. 2(4): 330-340.

Sobrado LF, Varone BB, Machado AD, Nearing BD, Zeng D, Belardinelli L and Verrier RL 2013. Dronedarone's inhibition of If current is the primary mechanism responsible for its bradycardic effect. J Cardiovasc Electrophysiol. 24(8): 914-918.

Stoykov I, van Beeren HC, Moorman AF, Christoffels VM, Wiersinga WM and Bakker O 2007. Effect of amiodarone and dronedarone administration in rats on thyroid

hormone-dependent gene expression in different cardiac components. Eur J Endocrinol. 156(6): 695-702.

Sun w, Sarma J and Singh B 2002. Chronic and acute effects of dronedarone on the action potential of rabbit atrial muscle preparations: comparison with amiodarone. J Cardiovas Pharm. 39: 677-684.

Sun W, Sarma JS and Singh BN 1999. Electrophysiological effects of dronedarone (SR33589), a noniodinated benzofuran derivative, in the rabbit heart : comparison with amiodarone. Circulation. 100(22): 2276-2281.

Talley RC, Meyer JF and McNay JL 1971. Evaluation of the pre-ejection period as an estimate of myocardial contractility in dogs. Am J Cardiol. 27(4): 384-391.

Task-Force. 1996. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 17(3): 354-381.

Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C and Biollaz J 2007. Effect of dronedarone on renal function in healthy subjects. Br J Clin Pharmacol. 64(6): 785-791.

Van Beeren HC, Jong WM, Kaptein E, Visser TJ, Bakker O and Wiersinga WM 2003. Dronerarone acts as a selective inhibitor of 3,5,3'-triiodothyronine binding to thyroid hormone receptor-alpha1: in vitro and in vivo evidence. Endocrinology. 144(2): 552-558.

Vanderlei LC, Pastre CM, Hoshi RA, Carvalho TD and Godoy MF 2009. Basic notions of heart rate variability and its clinical applicability. Rev Bras Cir Cardiovasc. 24(2): 205-217.

Vassallo P and Trohman RG 2007. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA. 298(11): 1312-1322.

Verduyn SC, Vos MA, Leunissen HD, van Opstal JM and Wellens HJ 1999. Evaluation of the acute electrophysiologic effects of intravenous dronedarone, an amiodarone-like agent, with special emphasis on ventricular repolarization and acquired torsade de pointes arrhythmias. J Cardiovasc Pharmacol. 33(2): 212-222.

Waldhauser KM, Torok M, Ha HR, Thomet U, Konrad D, Brecht K, Follath F and Krahenbuhl S 2006. Hepatocellular toxicity and pharmacological effect of amiodarone and amiodarone derivatives. J Pharmacol Exp Ther. 319(3): 1413-1423.

Ware WA, Muir WW and Swanson C 1991. Effects of amiodarone on myocardial performance in normal canine hearts and canine hearts with infarcts. Am J Vet Res. 52(6): 891-897.

Wiersinga WM 1997. Towards an animal model of amiodarone-induced thyroid dysfunction. Eur J Endocrinol. 137(1): 15-17.

Winchell RJ and Hoyt DB 1996. Spectral analysis of heart rate variability in the ICU: a measure of autonomic function. J Surg Res. 63(1): 11-16.

Yamreudeewong W, McIntyre WW, Sun TJ and Ranelli PL 2000. Bone marrow granulomas possibly associated with amiodarone. Pharmacotherapy. 20(7): 855-859.

Zhai H, Mu Y, Guan L and Li Y 2013. The value of aneurysm volume and myocardial strain rate for evaluating cardiac function of ischemia-related left ventricular aneurysm in a rabbit model using real time three-dimensional echocardiographic imaging combined with speckle tracking imaging. Echocardiography. 30(7): 837-842.

Zipes DP, Prystowsky EN and Heger JJ 1984. Amiodarone: electrophysiologic actions, pharmacokinetics and clinical effects. J Am Coll Cardiol. 3(4): 1059-1071.

APPENDIX

Complete blood count profile data of the present study

Table I white blood cell count (WBC) (10^3/uL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	4.94	5.28	4.15	DR01	5.17	4.31	4.70
AM02	5.35	5.05	6.76	DR02	9.22	7.24	5.47
AM03	7.21	5.84	5.04	DR03	4.20	4.96	4.55
AM05	5.15	4.48	4.10	DR04	6.48	4.82	4.49
AM06	6.53	4.20	4.33	DR05	5.84	5.62	5.02
AM07	5.15	4.77	5.17	DR06	10.48	10.02	8.17
AM09	4.30	4.36	3.99	DR07	3.09	3.61	4.10
AM10	4.51	4.62	4.90	DR08	4.34	5.11	4.06
MEAN	5.39	4.83	4.81	**MEAN**	6.10	5.71	5.07
SEM	0.35	0.19	0.32	**SEM**	0.90	0.72	0.47

Table II red blood cell count (RBC) (10^6/uL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	6.11	5.37	5.72	DR01	5.90	5.14	5.31
AM02	4.99	4.92	4.88	DR02	6.07	5.63	5.82
AM03	5.99	4.88	5.54	DR03	6.15	6.08	5.90
AM05	6.29	5.83	5.66	DR04	6.48	5.62	5.29
AM06	5.61	5.46	5.12	DR05	5.36	5.43	5.29
AM07	4.26	4.59	4.79	DR06	6.03	5.93	5.90
AM09	4.93	4.66	4.81	DR07	4.99	5.00	5.25
AM10	5.48	5.16	4.80	DR08	6.37	5.87	5.65
MEAN	5.46	5.11	5.17	**MEAN**	5.92	5.59	5.55
SEM	0.25	0.15	0.15	**SEM**	0.18	0.13	0.10

Table III hemoglobin (Hb) (g/dL) of the rabbits in amiodarone (upper) and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	11.7	10.5	11.2	DR01	11.6	10.4	10.9
AM02	10.5	10.6	10.5	DR02	12.5	11.9	12.2
AM03	12.4	10.3	11.8	DR03	12.4	12.4	12.2
AM05	12.8	11.9	11.9	DR04	11.6	11.9	11.6
AM06	11.2	11.0	10.5	DR05	10.8	11.1	10.7
AM07	9.0	9.9	10.3	DR06	11.3	11.0	11.0
AM09	9.4	8.9	9.3	DR07	10.4	10.3	10.5
AM10	11.5	10.9	10.1	DR08	12.9	11.9	11.5
MEAN	11.06	10.50	10.70	**MEAN**	11.69	11.36	11.33
SEM	0.48	0.31	0.31	**SEM**	0.31	0.27	0.23

Table IV hematocrit (Hct) (%) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	38.0	31.5	33.7	DR01	36.2	32.4	34.3
AM02	35.0	33	32.9	DR02	37.7	35.9	37.2
AM03	38.9	32.2	36.8	DR03	38.4	40.6	40.4
AM05	38.2	37.9	37.6	DR04	11.6	36.9	36.9
AM06	34.9	35.6	34.8	DR05	34.5	37.4	36.2
AM07	30.8	33.2	34.9	DR06	38.6	38.3	37.1
AM09	31.3	29.9	32.0	DR07	34.8	35.4	35.5
AM10	38.2	36.1	34.6	DR08	40.3	37.4	36.5
MEAN	35.66	33.68	34.66	**MEAN**	34.01	36.79	36.76
SEM	1.14	0.94	0.66	**SEM**	3.28	0.84	0.62

Table V mean corpuscular volume (MCV) (fL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	62.2	58.7	58.9	DR01	61.4	63.0	64.6
AM02	70.1	67.1	67.4	DR02	62.1	63.8	63.9
AM03	64.9	66.0	66.4	DR03	62.4	66.8	68.5
AM05	60.7	65.0	66.4	DR04	62.4	65.7	69.8
AM06	62.2	65.2	68.0	DR05	64.4	68.9	69.9
AM07	72.3	72.3	72.9	DR06	64.0	64.6	62.9
AM09	63.5	64.2	66.5	DR07	69.7	70.8	67.6
AM10	69.7	70.0	72.1	DR08	63.3	63.7	64.8
MEAN	65.70	66.06	67.33	**MEAN**	63.71	65.91	66.50
SEM	1.55	1.43	1.51	**SEM**	0.93	0.97	0.98

Table VI mean corpuscular hemoglobin (MCH) (pg) of the rabbits in amiodarone and dronedarone treated groups on day0, 7 and 14

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	19.1	19.6	19.6	DR01	19.7	20.2	20.5
AM02	21.0	21.5	21.5	DR02	20.6	21.1	21.0
AM03	20.7	21.1	21.3	DR03	20.2	20.4	20.7
AM05	20.3	20.4	21.0	DR04	21.2	21.2	21.9
AM06	20.0	20.1	20.5	DR05	20.1	20.4	20.7
AM07	21.1	21.6	21.5	DR06	18.7	18.5	18.6
AM09	19.1	19.1	19.3	DR07	20.8	20.6	20.0
AM10	21.0	21.1	21.0	DR08	20.3	20.3	20.4
MEAN	20.29	20.56	20.71	**MEAN**	20.20	20.34	20.48
SEM	0.29	0.32	0.30	**SEM**	0.27	0.29	0.33

Table VII mean corpuscular hemoglobin concentration (MCHC) (g/dL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	30.8	33.3	33.2	DR01	32.0	32.1	31.8
AM02	30.0	32.1	31.9	DR02	33.2	33.1	32.8
AM03	31.9	32.0	32.2	DR03	32.3	30.5	30.2
AM05	33.5	31.4	31.6	DR04	33.9	32.2	31.4
AM06	32.1	30.9	30.2	DR05	31.3	29.7	29.6
AM07	21.1	29.8	29.5	DR06	29.3	28.7	29.6
AM09	30.0	29.8	29.1	DR07	29.9	29.1	29.6
AM10	30.1	30.2	29.2	DR08	32.0	31.8	31.4
MEAN	29.94	31.19	30.86	**MEAN**	31.74	30.90	30.80
SEM	1.34	0.44	0.55	**SEM**	0.55	0.57	0.43

Table VIII platelet count (10^3/uL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	336	343	352	DR01	494	459	493
AM02	541	473	432	DR02	364	151	435
AM03	545	586	434	DR03	465	494	393
AM05	562	520	412	DR04	575	525	459
AM06	748	578	491	DR05	508	540	483
AM07	379	379	403	DR06	434	466	446
AM09	550	523	579	DR07	276	349	358
AM10	274	393	320	DR08	365	247	433
MEAN	491.88	474.38	427.88	**MEAN**	435.13	403.88	437.50
SEM	54.06	32.90	28.39	**SEM**	33.95	49.96	15.82

Table IX mean platelet volume (MPV) (fL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	7.1	7.3	7.8	DR01	6.7	6.6	6.9
AM02	7.0	6.8	7.2	DR02	6.4	7.7	6.8
AM03	6.4	6.4	6.9	DR03	7.5	7.3	7.2
AM05	7.1	7.4	7.2	DR04	7.2	7.1	6.5
AM06	7.0	6.9	6.8	DR05	7.2	7.2	7.5
AM07	7.6	7.2	7.8	DR06	6.9	6.7	6.9
AM09	7.7	7.8	8.1	DR07	7.5	7.5	8.0
AM10	7.4	6.9	7.7	DR08	7.3	7.9	7.4
MEAN	7.16	7.09	7.44	**MEAN**	7.09	7.25	7.15
SEM	0.15	0.15	0.17	**SEM**	0.14	0.16	0.17

Blood chemistry data of the present study

Table X aspartate aminotransferase (AST) levels (IU/L) of the rabbits in amiodarone and dronedarone treated groups on day0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	30.8	11.6	14.1	DR01	20.6	14.2	12.4
AM02	26.1	17.0	12.3	DR02	20.4	23.1	14.7
AM03	43.2	32.2	14.6	DR03	32.2	18.0	22.4
AM05	33.1	53.1	20.1	DR04	27.2	11.8	15.5
AM06	19.0	10.9	16.8	DR05	62.0	26.8	14.1
AM07	21.1	16.1	15.9	DR06	15.5	15.5	22.0
AM09	14.1	16.5	8.8	DR07	20.4	13.5	10.4
AM10	17.2	20.2	14.9	DR08	24.8	22.5	17.8
MEAN	25.58	22.20	14.69	**MEAN**	27.89	18.18	16.16
SEM	3.43	4.99	1.17	**SEM**	5.19	1.90	1.52

Table XI alanine aminotransferase (ALT) levels (IU/L) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	76.1	61.4	60.3	DR01	28.1	26.1	23.7
AM02	41.1	36.0	37.3	DR02	52.1	60.9	50.2
AM03	44.1	31.5	26.7	DR03	105.9	57.3	62.5
AM05	35.4	48.8	33.8	DR04	77.6	48.6	44.4
AM06	39.2	24.8	26.3	DR05	63.4	52.4	41.1
AM07	48.8	43.0	42.2	DR06	48.1	43.7	54.0
AM09	50.5	54.3	39.0	DR07	63.3	43.1	40.4
AM10	29.4	36.5	24.6	DR08	52.1	43.2	43.7
MEAN	45.58	42.04	36.28	**MEAN**	61.33	46.91	45.00
SEM	4.99	4.32	4.13	**SEM**	8.14	3.80	4.02

Table XII alkaline phosphatase (ALP) levels (IU/L) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	167.7	124.0	177.9	DR01	122.9	132.1	167.6
AM02	143.0	150.7	194.3	DR02	99.9	105.7	121.5
AM03	174.8	163.7	229.7	DR03	155.7	138.8	129.7
AM05	121.7	137.0	181.8	DR04	250.9	265.2	251.6
AM06	201.8	227.6	232.7	DR05	105.4	129.2	129.2
AM07	121.9	160.7	154.7	DR06	148.6	153.9	159.4
AM09	129.4	151.6	194.9	DR07	177.7	164.2	152.1
AM10	159.4	165.0	209.1	DR08	236.2	290.0	268.4
MEAN	152.46	160.04	196.89	**MEAN**	162.16	172.39	172.44
SEM	10.10	10.85	9.34	**SEM**	20.03	23.87	19.99

Table XIII gamma-glutamyl transferase (GGT) levels (IU/L) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	16.6	22.2	18.3	DR01	8.8	9.1	9.3
AM02	8.5	9.3	9.6	DR02	12.4	11.2	12.1
AM03	13.7	12.3	11.4	DR03	19.4	17.6	12.3
AM05	7.8	8.5	7.2	DR04	9.5	9.9	7.7
AM06	8.2	8.3	7.7	DR05	11.4	12.0	13.0
AM07	10.3	10.6	11.0	DR06	6.8	8.2	5.9
AM09	10.5	13.1	11.7	DR07	12.3	10.2	12.0
AM10	7.8	7.4	6.5	DR08	17.7	15.4	16.0
MEAN	10.43	11.46	10.43	**MEAN**	12.29	11.7o	11.04
SEM	1.13	1.69	1.33	**SEM**	1.53	1.14	1.14

Table XIV total protein (TP) levels (g/dL) of the rabbits in amiodarone and droedarone treated groups on Day 0, Day7 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	6.3	5.8	5.9	DR01	6.3	5.5	5.8
AM02	6.1	5.5	5.7	DR02	6.1	5.8	6.1
AM03	6.7	5.8	5.7	DR03	6.1	6.1	6.3
AM05	6.2	5.7	5.6	DR04	6.2	6.3	6.4
AM06	5.9	5.4	5.3	DR05	6.1	6.3	6.3
AM07	5.7	5.9	6.3	DR06	6.2	6.1	6.0
AM09	5.2	5.6	5.4	DR07	5.8	6.4	5.8
AM10	6.4	6.2	5.6	DR08	6.2	6.0	5.8
MEAN	6.06	5.74	5.69	**MEAN**	6.13	6.06	6.06
SEM	0.16	0.09	0.11	**SEM**	0.05	0.11	0.09

Table XV albumin (Alb) levels (g/dL) of the rabbits in amiodarone and dronedarone treated groups on Day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	5.4	5.2	5.0	DR01	5.1	4.5	5.2
AM02	4.8	4.6	5.0	DR02	5.7	5.0	5.6
AM03	5.7	5.0	4.9	DR03	4.0	3.8	3.8
AM05	4.1	3.7	3.6	DR04	3.9	3.9	3.9
AM06	3.8	3.4	3.4	DR05	3.9	3.8	3.8
AM07	3.7	3.8	4.0	DR06	3.5	3.5	3.7
AM09	3.3	3.6	3.7	DR07	3.5	3.8	3.7
AM10	3.7	3.8	3.8	DR08	3.5	3.6	3.7
MEAN	4.31	4.14	4.18	**MEAN**	4.14	3.99	4.18
SEM	0.31	0.24	0.24	**SEM**	0.29	0.18	0.27

Table XVI total bilirubin (TB) levels (mg/dL) of the rabbits in amiodarone and dronedarone treated groups on Day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.8	0.9	1.0	DR01	1.0	0.8	0.8
AM02	0.9	0.8	0.7	DR02	1.0	0.8	0.9
AM03	0.8	0.8	1.0	DR03	0.6	0.6	0.5
AM05	0.6	0.5	0.5	DR04	0.6	0.6	0.4
AM06	0.6	0.6	0.5	DR05	0.6	0.6	0.5
AM07	0.6	0.6	0.6	DR06	0.6	0.6	0.6
AM09	0.6	0.6	0.6	DR07	0.6	0.6	0.6
AM10	0.6	0.5	0.5	DR08	0.6	0.5	0.5
MEAN	0.69	0.66	0.68	**MEAN**	0.70	0.64	0.60
SEM	0.04	0.05	0.08	**SEM**	0.07	0.04	0.06

Table XVII direct bilirubin (DB) levels (mg/dL) of the rabbits in amiodarone and dronedarone treated groups on Day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.44	0.40	0.50	DR01	0.38	0.45	0.422
AM02	0.43	0.43	0.50	DR02	0.45	0.52	0.44
AM03	0.54	0.36	0.50	DR03	0.05	0.06	0.06
AM05	0.07	0.06	0.05	DR04	0.03	0.07	0.05
AM06	0.06	0.07	0.04	DR05	0.05	0.07	0.04
AM07	0.05	0.07	0.04	DR06	0.05	0.04	0.04
AM09	0.04	0.05	0.05	DR07	0.08	0.06	0.06
AM10	0.04	0.04	0.05	DR08	0.05	0.04	0.05
MEAN	0.21	0.19	0.22	**MEAN**	0.14	0.16	0.15
SEM	0.07	0.06	0.08	**SEM**	0.06	0.07	0.06

Table XVIII blood urea nitrogen (BUN) levels (mg/dL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	16.7	14.1	14.7	DR01	17.7	13.5	9.3
AM02	17.0	13.7	11.8	DR02	14.4	14.9	12.1
AM03	18.8	13.9	14.2	DR03	17.7	18.6	18.3
AM05	14.8	14.4	15.7	DR04	16.1	17.7	17.8
AM06	15.1	11.8	17.5	DR05	19.2	18.0	19.4
AM07	16.1	16.6	17.3	DR06	20.3	13.9	11.9
AM09	13.5	11.2	10.2	DR07	12.1	12.4	14.2
AM10	13.3	11.0	11.1	DR08	12.4	10.6	14.2
MEAN	15.66	13.34	14.06	**MEAN**	16.24	14.95	14.65
SEM	0.66	0.67	0.98	**SEM**	1.08	1.03	1.26

Table XIX serum creatinine (Cr) levels (mg/dL) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	1.0	0.9	0.9	DR01	0.9	0.8	0.8
AM02	0.7	0.7	0.7	DR02	1.0	0.9	0.9
AM03	1.1	0.9	1.0	DR03	0.9	1.0	1.0
AM05	0.6	0.8	0.7	DR04	0.8	0.9	0.8
AM06	0.8	0.7	0.7	DR05	0.9	0.9	0.8
AM07	0.9	0.9	0.8	DR06	1.3	1.2	1.2
AM09	0.6	0.6	0.8	DR07	0.6	0.9	1.2
AM10	0.8	0.9	0.9	DR08	0.6	0.7	0.8
MEAN	0.81	0.8o	0.81	**MEAN**	0.88	0.91	0.94
SEM	0.06	0.04	0.04	**SEM**	0.08	0.05	0.06

Thyroid profile data of the present study

Table XX total triiodothyronine (tT_3) levels (ng/dl)) of the rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	67.5	55.4	76.8	DR01	77.9	70.5	110.0
AM02	59.9	81.0	74.4	DR02	62.8	131.0	147.0
AM03	100.0	123.0	94.9	DR03	161.0	100.0	132.0
AM05	111.0	115.0	91.1	DR04	107.0	96.5	84.0
AM06	116.0	97.4	107	DR05	110	85.2	105.0
AM07	124.0	87.6	56.0	DR06	33.0	80.5	106.0
AM09	62.2	75.5	47.3	DR07	69.1	77.0	57.9
AM10	85.7	139.0	94.1	DR08	44.8	88.9	61.5
MEAN	90.79	96.74	80.20	**MEAN**	83.20	91.20	100.43
SEM	9.04	9.73	7.27	**SEM**	14.62	6.65	11.10

Table XXI total thyroxine (tT_4) levels (µg/dl)) of the rabbits in amiodarone and dronedarone treated group on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	8.9	12.4	14.6	DR01	7.7	4.2	4.8
AM02	4.4	9.4	11.1	DR02	3.3	3.3	2.5
AM03	8.2	12.4	14	DR03	5.3	4.1	4.4
AM05	10.5	11.6	11.3	DR04	7.7	5.5	4.3
AM06	8.2	13.3	12.4	DR05	8.9	7	4.7
AM07	6.8	9.3	9.6	DR06	6.3	7	7.2
AM09	3.2	10.2	11.5	DR07	6	4.6	4.5
AM10	5.0	14.4	13.3	DR08	5.2	6	3.8
MEAN	6.90	11.63	12.23	**MEAN**	6.30	5.21	4.53
SEM	0.89	0.66	0.59	**SEM**	0.63	0.49	0.46

Heart rate variability (HRV) data of the present study

Table XXII heart rate (BPM) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	194.9	201.3	166.4	DR01	216.1	214.9	200.1
AM02	185.8	226.1	229.7	DR02	228.5	201.0	216.6
AM03	249.3	190.9	184.2	DR03	211.6	197.1	175.4
AM05	212.4	199.1	203.4	DR04	225.5	226.2	211.4
AM06	232.6	200.0	202.2	DR05	191.9	218.1	182.4
AM07	198.9	181.6	172.3	DR06	181.9	169.0	153.6
AM09	241.4	196.2	183.8	DR07	207.6	215.4	184.0
AM10	233.6	202.3	195.7	DR08	199.8	196.8	183.1
MEAN	218.61	199.69	192.21	**MEAN**	207.86	204.81	188.33
SEM	8.40	14.49	7.12	**SEM**	5.69	6.37	7.23

Table XXIII total power (μs^2) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	253.1	201.1	200.3	DR01	256.9	244.6	195.6
AM02	263	216	140.4	DR02	236.8	191.5	51.27
AM03	134.9	172.7	103.3	DR03	331.1	310.4	195.4
AM05	228.7	200.3	179.2	DR04	216.9	71.07	32.45
AM06	197.8	209.8	212.4	DR05	182.5	179	189.8
AM07	253.5	127.1	106.2	DR06	232.9	292.8	279.5
AM09	92.63	82.79	67.86	DR07	125.9	85.04	73.84
AM10	120.9	120.1	105.3	DR08	145.6	82.66	81.60
MEAN	193.07	166.24	139.37	**MEAN**	216.08	182.13	137.43
SEM	23.95	17.64	18.57	**SEM**	23.08	33.90	31.42

Table XXIV very low frequency (VLF) (μs^2) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	176.3	66.28	87.27	DR01	113.50	149.40	101.90
AM02	138.4	52.08	55.9	DR02	93.06	63.17	27.77
AM03	62.82	59.38	31.27	DR03	177.4	168.8	97.52
AM05	60.23	146.5	79.52	DR04	161.1	31.29	20.61
AM06	90.72	68.61	117.1	DR05	100.00	43.42	99.98
AM07	134.4	31.13	58.59	DR06	85.72	102.60	156.90
AM09	55.63	27.01	19.5	DR07	40.90	52.87	47.08
AM10	18.69	27.68	21.75	DR08	27.44	22.08	23.49
MEAN	92.15	59.83	58.86	**MEAN**	99.89	79.20	71.91
SEM	18.72	13.77	12.19	**SEM**	18.38	19.49	17.48

Table XXV low frequency (LF) (us^2) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	69.99	109.1	65.81	DR01	136.50	92.31	43.73
AM02	95.21	80.75	42.24	DR02	80.39	81.68	16.37
AM03	64.11	60.94	42.04	DR03	137.40	147.5	72.45
AM05	144.9	42.94	60.69	DR04	46.54	32.64	9.055
AM06	89.07	125.1	82.29	DR05	69.52	97.66	59.30
AM07	122.9	90.01	42.47	DR06	98.33	71.51	52.39
AM09	43.95	49.64	26.57	DR07	72.84	18.78	17.84
AM10	65.01	72.57	57.58	DR08	96.58	28.30	25.11
MEAN	86.89	78.88	52.46	**MEAN**	92.26	71.29	37.03
SEM	11.85	10.08	6.19	**SEM**	11.32	15.33	8.18

Table XXVI high frequency (HF) (us^2) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	15.71	28.43	48.07	DR01	30.04	19.98	54.77
AM02	30.04	84.79	50.44	DR02	69.38	57.54	8.57
AM03	8.133	54.14	30.75	DR03	19.84	30.83	29.4
AM05	24.64	11.44	39.43	DR04	11.42	12.04	4.52
AM06	20.20	18.09	19.43	DR05	17.41	41.17	32.15
AM07	12.95	12.56	7.062	DR06	58.12	119.5	74.3
AM09	4.73	9.63	23.35	DR07	15.86	13.58	9.86
AM10	38.65	23.8	28.3	DR08	28.51	33.86	33.08
MEAN	19.38	30.36	30.85	**MEAN**	31.32	41.06	30.83
SEM	4.03	9.29	5.20	**SEM**	7.48	12.41	8.56

Table XXVII low to high frequency ratio (LF/HF) (%) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	4.46	3.84	1.37	DR01	4.55	4.12	0.79
AM02	3.17	0.95	0.84	DR02	1.15	1.42	1.91
AM03	7.88	1.13	1.37	DR03	6.93	4.78	2.46
AM05	5.88	3.75	1.54	DR04	4.08	2.71	2.00
AM06	4.43	6.92	4.24	DR05	3.99	2.37	1.85
AM07	9.49	7.17	6.01	DR06	1.69	0.59	0.71
AM09	6.13	5.15	1.14	DR07	4.59	1.38	1.81
AM10	1.68	3.05	2.04	DR08	3.39	0.84	0.76
MEAN	5.39	3.99	2.32	**MEAN**	3.79	2.28	1.54
SEM	0.89	0.83	0.65	**SEM**	0.64	0.54	0.24

Standard echocardiography parameters of the present study

Table XXVIII ejection fraction (EF) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	79.48	72.85	70.15	DR01	48.17	65.50	62.77
AM02	79.94	68.70	60.14	DR02	66.48	52.74	72.43
AM03	79.13	70.10	71.00	DR03	65.70	57.47	66.11
AM05	74.14	78.54	60.24	DR04	67.76	59.12	48.75
AM06	62.84	69.90	75.51	DR05	60.66	65.19	70.95
AM07	64.06	67.19	75.87	DR06	70.68	66.75	66.51
AM09	70.79	72.17	67.72	DR07	69.15	67.37	67.30
AM10	59.39	72.67	58.81	DR08	59.99	76.39	58.51
MEAN	71.22	71.52	67.43	**MEAN**	63.57	63.82	64.17
SEM	2.92	1.23	2.45	**SEM**	2.57	2.57	2.69

Table XXIX fractional shortening (FS) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	43.75	38.59	36.49	DR01	22.06	33.15	31.11
AM02	40.29	35.09	29.51	DR02	33.55	24.50	38.41
AM03	43.68	35.88	36.55	DR03	33.13	27.41	33.33
AM05	39.46	43.36	29.49	DR04	34.44	28.35	22.22
AM06	31.10	36.13	40.70	DR05	29.56	32.72	37.13
AM07	31.85	34.00	41.38	DR06	36.60	33.54	33.50
AM09	36.78	37.91	34.69	DR07	35.65	34.12	33.73
AM10	28.25	38.51	28.33	DR08	29.00	41.07	28.17
MEAN	36.89	37.43	34.64	**MEAN**	31.75	31.86	32.20
SEM	2.09	1.03	1.80	**SEM**	1.68	1.80	1.82

Table XXX pre-ejection period to ejection time ratio (PEP/ET) of the conscious rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.23	0.17	0.21	DR01	0.24	0.12	0.24
AM02	0.24	0.22	0.19	DR02	0.26	0.17	0.17
AM03	0.25	0.18	0.25	DR03	0.23	0.24	0.19
AM05	0.14	0.21	0.13	DR04	0.26	0.17	0.19
AM06	0.17	0.27	0.15	DR05	0.25	0.25	0.19
AM07	0.19	0.14	0.17	DR06	0.20	0.11	0.19
AM09	0.20	0.17	0.21	DR07	0.15	0.22	0.17
AM10	0.23	0.22	0.21	DR08	0.17	0.16	0.15
MEAN	0.21	0.19	0.19	**MEAN**	0.22	0.18	0.19
SEM	0.01	0.01	0.01	**SEM**	0.01	0.02	0.01

Table XXXI isovolumic contraction time (IVCT) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	55	59	56	DR01	55	53	43
AM02	50	46	53	DR02	61	40	48
AM03	57	49	41	DR03	55	49	49
AM05	35	49	42	DR04	50	34	47
AM06	54	48	36	DR05	37	59	52
AM07	51	55	47	DR06	61	55	35
AM09	53	47	45	DR07	45	50	51
AM10	49	40	63	DR08	53	53	45
MEAN	50.50	49.13	47.88	**MEAN**	52.13	49.13	46.25
SEM	2.41	2.03	3.14	**SEM**	2.86	2.91	1.92

Table XXXII isovolumic relaxation time (IVRT) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	42	41	46	DR01	56	57	43
AM02	43	65	52	DR02	42	41	46
AM03	57	57	61	DR03	51	54	55
AM05	47	43	54	DR04	50	62	52
AM06	55	51	56	DR05	56	48	60
AM07	58	57	61	DR06	47	58	54
AM09	62	65	55	DR07	60	57	58
AM10	66	59	51	DR08	56	58	69
MEAN	53.75	54.75	54.50	**MEAN**	52.25	54.38	54.63
SEM	3.13	3.22	1.78	**SEM**	2.08	2.38	2.89

Table XXXIII Tei index echocardiography parameter of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.76	0.75	1.24	DR01	0.90	0.92	0.68
AM02	0.93	0.69	0.83	DR02	0.79	0.63	0.78
AM03	0.94	0.73	0.71	DR03	0.74	0.78	0.72
AM05	0.64	0.63	0.64	DR04	0.69	0.59	0.69
AM06	0.82	0.80	0.62	DR05	0.68	0.77	0.82
AM07	0.81	0.86	0.79	DR06	0.92	0.75	0.65
AM09	0.89	0.81	0.78	DR07	0.84	0.79	0.69
AM10	0.82	0.74	0.91	DR08	0.75	0.78	0.77
MEAN	0.83	0.75	0.81	**MEAN**	0.79	0.75	0.73
SEM	0.03	0.02	0.07	**SEM**	0.03	0.04	0.02

Speckle tracking echocardiography parameters of the present study

Table XXXIV fractional area change (FAC) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	28.44	29.01	24.29	DR01	21.47	22.12	22.06
AM02	32.12	24.02	20.15	DR02	26.03	23.05	31.13
AM03	24.26	19.24	26.93	DR03	18.59	19.13	21.16
AM05	26.46	16.07	22.15	DR04	21.30	19.74	24.57
AM06	24.04	23.48	31.27	DR05	16.84	22.44	23.20
AM07	17.58	21.63	20.16	DR06	24.72	30.92	23.27
AM09	23.89	26.40	21.40	DR07	28.51	24.93	25.00
AM10	25.40	22.56	26.89	DR08	27.77	21.47	27.46
MEAN	25.27	22.80	24.16	**MEAN**	23.15	22.98	24.73
SEM	1.48	1.42	1.39	**SEM**	1.51	1.31	1.14

Table XXXV time to peak standard deviation of speed (speed_TPSD) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	19.09	44.45	26.62	DR01	41.59	41.95	29.58
AM02	32.11	51.49	37.74	DR02	28.14	28.10	30.25
AM03	42.82	55.72	47.38	DR03	25.13	42.09	51.01
AM05	45.70	27.05	28.78	DR04	31.38	28.67	30.49
AM06	31.91	26.14	27.01	DR05	30.19	24.60	28.63
AM07	58.73	21.27	41.35	DR06	33.54	34.71	29.77
AM09	16.89	34.19	28.46	DR07	26.17	31.03	17.93
AM10	37.65	24.87	35.48	DR08	22.24	30.58	22.13
MEAN	35.61	35.65	34.10	**MEAN**	29.79	32.72	29.97
SEM	4.89	4.67	2.71	**SEM**	2.12	2.27	3.41

Table XXXVI time to peak Standard Deviation of global displacement (displace_TPSD) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	40.41	18.53	27.41	DR01	17.42	20.96	20.64
AM02	26.64	25.09	26.55	DR02	11.37	15.22	21.65
AM03	16.37	33.06	23.9	DR03	34.23	16.29	37.76
AM05	35.53	28.9	27.52	DR04	10.81	16.5	16.05
AM06	24.23	20.25	31.47	DR05	27.62	20.58	30.23
AM07	30.79	27.41	25.41	DR06	4.23	18.89	23.85
AM09	21.46	25.26	24.23	DR07	11.10	17.29	5.07
AM10	10.66	37.43	13.75	DR08	21.73	33.34	20.75
MEAN	25.76	26.99	25.03	**MEAN**	17.31	19.88	22.00
SEM	3.47	2.21	1.82	**SEM**	3.53	2.06	3.39

Table XXXVII global radial plane strain parasternal short axis at basal segmental level (GRPS_PSAXB) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.15	0.16	1.44	DR01	4.72	8.33	5.97
AM02	6.46	4.45	8.22	DR02	6.32	1.56	1.07
AM03	4.84	4.45	3.01	DR03	7.51	2.32	4.25
AM05	4.05	10.46	3.24	DR04	2.76	2.10	2.89
AM06	4.52	5.48	3.52	DR05	1.72	3.03	3.19
AM07	6.67	0.32	1.12	DR06	0.14	4.89	7.24
AM09	2.29	8.83	0.11	DR07	6.15	2.48	1.07
AM10	5.16	1.07	0.87	DR08	4.60	5.09	7.58
MEAN	4.27	4.40	2.69	**MEAN**	4.24	3.73	4.16
SEM	0.76	1.36	0.90	**SEM**	0.89	0.79	0.91

Table XXXVIII global radial plane strain parasternal short axis at middle segmental level (GRPS_PSAXM) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	8.87	6.36	4.75	DR01	10.85	11.35	15.76
AM02	5.02	7.69	10.45	DR02	14.58	12.86	9.8
AM03	13.99	11.92	13.05	DR03	1.32	9.04	5.26
AM05	18.71	17.05	11.19	DR04	10.21	12.75	8.46
AM06	12.84	9.19	17.87	DR05	12.28	3.05	8.26
AM07	9.02	4.88	9.43	DR06	6.84	8.94	19.84
AM09	11.46	9.82	6.61	DR07	24.59	24.77	26.48
AM10	9.59	12.26	14.53	DR08	14.76	7.01	6.96
MEAN	11.19	9.89	10.99	**MEAN**	11.93	11.22	12.60
SEM	1.45	1.36	1.49	**SEM**	2.38	2.25	2.62

Table XXXIX global radial plane strain parasternal short axis at apical segmental level (GRPS_PSAXAP) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	4.42	1.61	6.33	DR01	7.84	8.71	10.98
AM02	6.57	4.75	8.36	DR02	17.56	9.98	10.01
AM03	14.62	17.29	17.18	DR03	5.80	9.56	10.27
AM05	8.78	8.48	5.12	DR04	10.63	15.09	16.08
AM06	8.66	7.21	20.86	DR05	12.84	5.82	15.81
AM07	7.44	6.34	10.69	DR06	17.33	28.02	16.92
AM09	11.81	14.30	4.20	DR07	16.45	9.09	17.72
AM10	27.56	15.13	15.82	DR08	13.84	8.84	10.45
MEAN	11.22	9.39	11.07	**MEAN**	12.79	11.89	13.53
SEM	2.58	1.97	2.19	**SEM**	1.56	2.48	1.19

Table XL global radial plane strain averaging (GRPS_Avg) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	4.48	2.71	4.17	DR01	7.81	9.46	10.91
AM02	6.01	5.63	9.01	DR02	12.82	8.13	9.88
AM03	11.15	21.22	11.08	DR03	4.88	6.97	6.59
AM05	10.51	11.99	6.51	DR04	7.87	9.31	11.48
AM06	8.68	7.29	14.08	DR05	8.94	3.96	9.09
AM07	7.71	3.85	7.08	DR06	8.10	13.95	14.66
AM09	8.52	10.99	3.64	DR07	15.73	12.11	15.09
AM10	14.1	9.49	10.41	DR08	11.07	6.98	8.33
MEAN	8.89	9.15	8.25	**MEAN**	9.65	8.86	10.75
SEM	1.07	2.08	1.26	**SEM**	1.20	1.11	1.05

Table XLI time to peak standard deviation of radial strain (GRPS_TPSD) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	61.15	68.71	73.45	DR01	50.77	42.56	38.81
AM02	66.11	59.8	44.78	DR02	17.56	58.85	46.68
AM03	47.92	59.44	48.75	DR03	51.16	46.48	68.09
AM05	43.53	32.98	10.00	DR04	49.17	53.39	64.17
AM06	39.89	46.49	48.70	DR05	59.32	52.38	52.8
AM07	64.60	65.69	70.35	DR06	59.49	44.73	41.37
AM09	49.56	48.81	59.08	DR07	48.65	51.33	50.15
AM10	52.90	53.47	61.42	DR08	28.08	53.83	42.46
MEAN	53.21	54.42	52.07	**MEAN**	45.53	50.44	50.57
SEM	3.46	4.09	7.04	**SEM**	5.27	1.92	3.78

Table XLII global circumferential plane strain parasternal short axis at basal segmental level (GCPS_PSAXB) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	-11.49	-17.31	-15.16	DR01	-9.63	-11.78	-12.53
AM02	-15.51	-11.51	-12.04	DR02	-12.23	-14.71	-13.92
AM03	-12.24	-8.21	-15.05	DR03	-6.58	-9.35	-8.43
AM05	-14.88	-5.27	-11.80	DR04	-13.04	-8.73	-10.55
AM06	-13.87	-12.35	-12.15	DR05	-11.94	-9.70	-11.65
AM07	-9.44	-10.85	-10.35	DR06	-12.32	-16.96	-10.31
AM09	-13.18	-14.79	-13.59	DR07	-13.13	-12.69	-15.69
AM10	-12.37	-12.67	-16.13	DR08	-16.65	-9.04	-11.65
MEAN	-12.87	-11.62	-13.28	**MEAN**	-11.94	-11.62	-11.84
SEM	0.69	1.31	0.71	**SEM**	1.03	1.06	0.79

Table XLIII global circumferential plane strain parasternal short axis at middle segmental level (GCPS_PSAXM) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	-12.79	-16.34	-13.53	DR01	-11.22	-11.25	-9.16
AM02	-16.41	-14.63	-7.01	DR02	-13.36	-13.11	-13.73
AM03	-8.89	-9.07	-9.37	DR03	-8.16	-8.52	-9.55
AM05	-12.4	-8.53	-9.12	DR04	-10.52	-8.00	-12.53
AM06	-11.24	-13.85	-14.43	DR05	-8.61	-9.77	-11.98
AM07	-8.04	-11.46	-9.90	DR06	-12.26	-12.91	-9.37
AM09	-12.45	-9.19	-11.74	DR07	-12.65	-13.73	-11.22
AM10	-10.72	-7.79	-13.39	DR08	-12.39	-12.74	-10.56
MEAN	-11.62	-11.36	-11.06	**MEAN**	-11.15	-11.25	-11.01
SEM	0.91	1.14	0.92	**SEM**	0.68	0.79	0.58

Table XLIV global circumferential plane strain parasternal short axis at apical segmental level (GCPS_PSAXAP) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	-16.75	-11.05	-8.38	DR01	-9.68	-8.57	-10.14
AM02	-12.94	-9.73	-7.55	DR02	-11.68	-6.87	-8.34
AM03	-10.37	-6.46	-14.42	DR03	-10.85	-10.95	-8.18
AM05	-9.53	-9.32	-5.69	DR04	-9.02	-8.57	-8.82
AM06	-12.47	-9.92	-12.3	DR05	-4.75	-9.08	-9.64
AM07	-9.2	-8.54	-10.38	DR06	-11.88	-11.31	-12.35
AM09	-10.63	-11.82	-8.08	DR07	-10.11	-8.92	-10.11
AM10	-12.65	-10.88	-7.74	DR08	-9.34	-7.60	-16.66
MEAN	-11.82	-9.72	-9.32	**Mean**	-9.66	-8.98	-10.53
SEM	0.87	0.59	1.01	**SEM**	0.79	0.54	0.99

Table XLV global circumferential plane strain averaging (GCPS_Avg) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	-13.67	-14.9	-12.36	DR01	-10.18	-10.53	-10.61
AM02	-14.95	-11.95	-8.86	DR02	-12.42	-11.56	11.53
AM03	-10.5	-7.91	-12.95	DR03	-8.53	-9.61	-8.72
AM05	-12.27	-7.71	-8.87	DR04	-10.86	-8.43	-10.63
AM06	-12.53	-12.04	-12.96	DR05	-8.43	-9.52	-11.09
AM07	-8.89	-10.28	-10.21	DR06	-12.15	-13.73	-10.68
AM09	-12.09	-11.93	-11.14	DR07	-11.96	-11.78	-12.34
AM10	-11.91	-10.45	-12.42	DR08	-12.79	-9.79	-12.96
MEAN	-12.10	-10.89	-11.22	**MEAN**	-10.92	-10.62	-8.19
SEM	0.65	0.84	0.61	**SEM**	0.61	0.59	2.85

Table XLVI circumferential strain time-to-peak standard deviation (GCPS_TPSD) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	21.25	19.49	18.25	DR01	19.69	18.71	13.56
AM02	24.03	40.91	21.32	DR02	12.95	42.73	35.70
AM03	10.47	35.34	33.29	DR03	39.84	9.72	29.03
AM05	13.14	24.39	32.56	DR04	19.41	22.34	15.53
AM06	13.36	9.25	23.12	DR05	19.25	9.81	12.86
AM07	26.88	18.36	21.73	DR06	19.44	9.03	15.99
AM09	42.54	22.22	11.42	DR07	17.86	18.19	7.64
AM10	7.28	20.54	15.78	DR08	12.80	23.50	16.52
MEAN	19.87	23.81	22.18	**MEAN**	20.16	19.25	18.35
SEM	4.05	3.53	2.69	**SEM**	2.99	3.93	3.27

Table XLVII global radial plane strain rate parasternal short axis basal segmental level (GRPSR_PSAXB) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	2.99	1.11	1.87	DR01	2.68	3.71	1.85
AM02	3.40	2.07	6.00	DR02	1.70	1.70	1.83
AM03	1.22	0.52	5.42	DR03	3.97	1.73	1.09
AM05	1.53	4.28	0.81	DR04	3.76	1.11	1.73
AM06	1.87	2.40	1.65	DR05	3.57	1.52	1.83
AM07	2.06	1.18	3.18	DR06	2.37	2.07	2.887
AM09	2.34	3.24	0.92	DR07	1.43	1.48	2.26
AM10	2.18	2.42	1.41	DR08	3.38	2.11	3.08
MEAN	2.19	2.15	2.66	**MEAN**	2.86	1.93	2.07
SEM	0.25	0.43	0.72	**SEM**	0.34	0.28	0.23

Table XLVIII global radial plane strain rate parasternal short axis at middle segmental level (GRPSR_PSAXM) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	2.01	1.91	1.62	DR01	2.91	1.91	3.85
AM02	1.85	4.93	4.07	DR02	2.79	2.81	2.64
AM03	2.63	3.03	3.16	DR03	2.31	1.83	1.56
AM05	4.22	4.17	2.42	DR04	3.14	2.34	1.68
AM06	3.03	1.92	3.09	DR05	2.53	1.70	1.88
AM07	3.55	1.51	2.77	DR06	2.03	3.45	3.08
AM09	3.28	2.09	2.33	DR07	3.40	3.63	4.33
AM10	1.90	1.79	2.74	DR08	3.08	1.48	2.85
MEAN	2.81	2.67	2.78	**MEAN**	2.77	2.39	2.73
SEM	0.31	0.45	0.25	**SEM**	0.16	0.29	0.36

Table XLIX global radial plane strain rate parasternal short axis at apical segmental level (GRPSR_PSAXAP) (%) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	2.58	1.76	2.0	DR01	1.07	2.05	2.31
AM02	1.36	9.13	2.48	DR02	3.06	2.53	2.45
AM03	2.94	2.79	4.09	DR03	1.54	2.34	1.57
AM05	2.30	1.43	1.64	DR04	3.24	3.28	3.23
AM06	3.12	4.42	3.1	DR05	3.44	1.59	3.71
AM07	2.18	2.88	2.41	DR06	2.45	3.81	2.51
AM09	4.79	3.28	1.44	DR07	2.84	1.89	2.48
AM10	3.47	3.07	3.16	DR08	2.52	2.63	2.85
MEAN	2.84	3.59	2.54	**MEAN**	2.52	2.52	2.64
SEM	0.36	0.85	0.31	**SEM**	0.29	0.26	0.23

Table L global radial plane strain rate averaging (GRPSR_Avg) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	2.53	1.60	1.83	DR01	2.22	2.55	2.67
AM02	2.20	5.38	4.18	DR02	2.52	2.35	2.4
AM03	2.26	5.11	4.23	DR03	2.61	1.97	1.41
AM05	2.69	3.29	1.62	DR04	3.38	2.25	2.21
AM06	2.67	2.92	2.61	DR05	3.18	1.60	2.47
AM07	2.60	1.86	2.79	DR06	2.29	3.11	2.82
AM09	3.47	2.87	1.57	DR07	2.55	2.33	3.14
AM10	2.52	2.43	2.44	DR08	2.99	2.07	2.93
MEAN	2.62	3.18	2.66	**MEAN**	2.72	2.28	2.51
SEM	0.14	0.49	0.37	**SEM**	0.15	0.16	0.19

Table LI time to peak standard deviation of radial strain rate (GRPSR_TPSD) (ms) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	32.81	54.26	37.64	DR01	43.70	27.61	25.17
AM02	26.77	64.61	42.09	DR02	19.68	60.71	48.72
AM03	33.01	26.94	23.75	DR03	29.57	46.76	53.16
AM05	39.42	18.98	22.75	DR04	38.85	34.36	42.32
AM06	28.03	36.46	44.36	DR05	46.86	44.85	36.89
AM07	59.47	36.06	39.31	DR06	52.60	31.48	40.76
AM09	36.21	19.58	42.41	DR07	29.18	34.71	33.65
AM10	35.14	44.65	35.58	DR08	27.14	25.51	35.15
MEAN	36.36	37.69	35.99	**MEAN**	35.95	38.25	39.48
SEM	3.61	5.74	2.95	**SEM**	3.99	4.16	3.12

Table LII global circumferential plane strain rate parasternal short axis at basal segmental level (GCPSR_PSAXB) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.51	0.07	0.30	DR01	0.21	0.20	-0.02
AM02	0.38	0.25	0.57	DR02	0.11	0.30	0.43
AM03	0.37	0.40	0.05	DR03	-0.12	0.45	0.46
AM05	0.64	0.51	0.17	DR04	0.24	0.25	0.26
AM06	0.15	0.02	0.32	DR05	0.13	0.33	0.29
AM07	0.40	-0.1	0.17	DR06	0.77	0.50	0.14
AM09	0.37	0.10	-0.03	DR07	0.39	0.16	0.09
AM10	0.63	0.38	0.46	DR08	0.06	0.30	0.22
MEAN	0.431	0.204	0.251	**MEAN**	0.224	0.311	0.234
SEM	0.057	0.076	0.071	**SEM**	0.094	0.041	0.058

Table LIII global circumferential plane strain rate parasternal short axis at middle segmental level (GCPSR_PSAXM) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	0.77	0.19	0.19	DR01	0.27	0.22	0.36
AM02	0.23	0.28	0.18	DR02	-0.16	0.04	0.19
AM03	0.43	0.36	-0.11	DR03	0.56	0.36	0.39
AM05	0.36	0.37	0.20	DR04	0.38	0.28	0.28
AM06	0.09	0.59	0.08	DR05	0.50	0.25	0.40
AM07	0.33	0.17	0.13	DR06	0.22	0.36	0.12
AM09	0.21	0.42	0.20	DR07	0.12	0.02	0.13
AM10	0.21	0.43	0.20	DR08	0.10	0.19	0.35
MEAN	0.329	0.351	0.134	**MEAN**	0.249	0.215	0.278
SEM	0.073	0.049	0.038	**SEM**	0.083	0.046	0.0401

Table LIV global circumferential plane strain rate parasternal short axis at apical segmental level (GCPSR_PSAXAP) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	1.85	0.82	0.27	DR01	0.13	0.28	0.25
AM02	0.03	0.93	0.62	DR02	0.20	0.44	0.36
AM03	0.67	0.29	0.11	DR03	0.47	0.46	0.47
AM05	0.23	0.24	0.50	DR04	0.46	0.07	0.53
AM06	0.34	0.77	0.30	DR05	0.30	0.15	0.41
AM07	0.57	0.52	0.41	DR06	0.00	0.10	0.08
AM09	0.22	0.23	0.09	DR07	0.36	0.26	0.12
AM10	0.21	0.08	0.05	DR08	0.31	0.56	0.11
MEAN	0.515	0.485	0.294	**MEAN**	0.279	0.290	0.291
SEM	0.204	0.113	0.073	**SEM**	0.057	0.064	0.062

Table LV global circumferential plane strain rate averaging (GCPSR_Avg) (1/s) of the anesthetized rabbits in amiodarone and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	1.04	0.36	0.25	DR01	0.20	0.23	0.20
AM02	0.21	0.49	0.46	DR02	0.05	0.26	0.15
AM03	0.49	0.35	0.02	DR03	0.30	0.42	0.44
AM05	0.41	0.37	0.29	DR04	0.36	0.20	0.36
AM06	0.20	0.46	0.23	DR05	0.31	0.24	0.37
AM07	0.44	0.2	0.24	DR06	0.33	0.32	0.11
AM09	0.26	0.25	0.09	DR07	0.29	0.15	0.11
AM10	0.35	0.3	0.24	DR08	0.16	0.35	0.23
MEAN	0.425	0.347	0.228	**MEAN**	0.250	0.271	0.246
SEM	0.096	0.035	0.046	**SEM**	0.037	0.031	0.045

Table LVI time to peak standard deviation of circumferential strain rate (GCPSR_TPSD) (ms) of the anesthetized rabbits in amiodaronen and dronedarone treated groups on day 0, 7 and 14 in the present study

Rabbit ID	Day0	Day7	Day14	Rabbit ID	Day0	Day7	Day14
AM01	63.75	61.33	76.19	DR01	72.78	58.82	55.86
AM02	35.64	72.0	47.0	DR02	59.01	61.42	60.34
AM03	62.93	75.19	51.69	DR03	55.35	51.43	84.76
AM05	34.62	37.59	20.33	DR04	61.31	64.66	72.31
AM06	19.16	50.61	68.92	DR05	52.13	45.41	59.35
AM07	74.9	69.67	62.51	DR06	33.72	62.66	66.78
AM09	61.79	62.79	66.61	DR07	60.7	62.34	45.96
AM10	64.35	63.07	59.65	DR08	67.53	65.07	29.73
MEAN	52.14	61.53	56.61	**MEAN**	57.82	58.98	59.39
SEM	6.92	4.35	6.14	**SEM**	4.14	2.47	5.88

VITA

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Conference proceeding;

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