Preface

The present dissertation describes the experimental work carried out during February – April 2012, and is submitted to The Faculty of Health and Medical Sciences – Department of Large Animal Sciences – University of Copenhagen as part of the requirements for obtaining the master's degree in veterinary medicine. The thesis accounts for 30 ECTS points and is directed at anyone who has an interest in equine cardiology.

The thesis consists of a theoretical background followed by an experimental study. As a theoretical foundation is crucial in the understanding of equine cardiology, the theoretical basis of this thesis is deliberately made very thoroughly. The thesis is written in English for future publication.

I would like to thank all the people who helped me in the process of making this thesis. A special acknowledgement goes to my two project supervisors; Associate Professor Rikke Buhl, DVM, PhD, and Maria Mathilde Haugaard, DVM, PhD-student, at the Department of Large Animal Sciences, for their indispensable help, guidance and contagious enthusiasm throughout the project.
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Abbreviations

aERP: atrial effective refractory period

AF: Atrial fibrillation

AVN: Atrio-ventricular node

BCL: Basic cycle length

Ca_v channel: Voltage-gated calcium channel

CV: Conduction velocity

ECG: Electrocardiogram

ERG1 potassium channel: Ether a go-go related gene 1 potassium channel

HR: Heart rate

I_{ca}: Inward calcium current

$I_{K1:}$ Inward rectifier potassium current

I_{Kr}: Rapid delayed rectifier potassium current

$I_{Ks:}$ Slow delayed rectifier potassium current

$I_{Kur:}$ Ultra rapid potassium current

I_{Na}: Inward sodium current

$I_{To,\ f:}$ Fast transient outward potassium current

JTc: JT corrected

K_{ir}: Inward rectifier potassium channel

K_v channel: Voltage-gated potassium channel

LQTS: Long QT syndrome

Na_v channel: Voltage-gated sodium channel

PW: Pulse width

QTc: QT corrected

RP: refractory period

SAN: Sino-atrial node

SK channel: Small conductance calcium activated potassium channel

WL: Wave length

Abstract

This master's thesis investigates the effect of two different drugs on the QT interval on the electrocardiogram, and thereby assesses their antiarrhythmic potentials in equine cardiology. The thesis is divided into two sections; Part I comprises the theoretical foundation and Part II is an experimental study.

Part I – A review on electrophysiology focusing on principles of ionic basis of the cardiac action potential as well as impulse conduction within the heart is given. Furthermore, correlation between phases of the cardiac action potential and the surface electrocardiogram with special focus on the QT interval is presented. Finally, an overview of atrial fibrillation in horses including mechanism, classification and treatment of the arrhythmia is given.

Current options for treating atrial fibrillation in horses are limited due to moderate efficacy. Moreover, existing treatments may lead to severe side effects, including prolongation of the QT interval. Prolongation of the QT interval has been associated with life-threatening ventricular proarrhythmia. Therefore, in an attempt to avoid ventricular proarrhythmia, progressing focus on atrial-selectivity has developed. SK channels have recently been discovered to be specifically expressed in the atria, and inhibition of SK channels has been demonstrated to prevent and terminate atrial fibrillation in rabbits, guinea pigs and rats without affecting the QT interval. Thus, SK channel inhibition is a promising new therapeutic target in the treatment of atrial fibrillation. So far, inhibition of SK channels, in the treatment of atrial fibrillation in horses, has never been investigated. Hence, the purpose of the thesis has been to investigate the antiarrhythmic potential of a new SK negative modulator, NS8593, and a well-known sodium channel blocker called flecainide acetate, for treating atrial fibrillation in horses.

Part II - **Materials and method:** Six healthy horses were first enrolled in a standing transvenous procedure (conscious study). After a wash-out period of 2-11 days, the horses underwent a transvenous procedure in anesthesia (unconscious study). *Conscious study*: The horses received 2 mg/kg IV of flecainide. *Unconscious study*: Two horses were given 2 mg/kg IV of flecainide, while four horses were given 5 mg/kg IV of NS8593. Electrocardiograms were recorded during sinus rhythm and during programmed electrical stimulation at baseline and after administration of the

antiarrhythmic drug. QTc intervals were measured by ECG before, during and after drug infusion. **Results:** *Conscious study:* Flecainide was well tolerated by all horses. Four horses receiving flecainide in atrial fibrillation converted to sinus rhythm with an average time of 4.77 ±1.76 minutes. The QTc interval was significantly prolonged ($P<0.05$) within 15, 20 and 25 minutes post administration of flecainide. In addition, the QRS intervals were significantly prolonged ($P<0.05$) within 10, 15, 20 and 25 minutes post infusion of flecainide. The JTc interval was prolonged within 15, 20 and 25 minutes after flecainide infusion. Also, an increase in HR within 15, 20 and 25 minutes was observed post flecainide infusion. *Unconscious study:* Convulsions were observed in three of four horses receiving NS8593. One of two horses receiving flecainide in atrial fibrillation converted after 14.08 minutes. All horses receiving NS8593 in atrial fibrillation converted to sinus rhythm with an average time of 10.22 ± 1.87 minutes. There was no significant ($P>0.05$) QTc prolongation post administration of NS8593. A non-significant increase ($P>0.05$) in HR was observed within 20, 25 and 30 minutes after NS8593 infusion. **Conclusion:** Flecainide was well tolerated by all horses. The observed QTc prolongation was mainly the result of a QRS widening. The increase in the JTc interval at higher heart rates was suggested to be caused by the QT correction method used in the study. Flecainide is therefore a safe and effective antiarrhythmic agent for treating atrial fibrillation in horses at the dosage of 2 mg/kg. In the unconscious study NS8593 converted horses in atrial fibrillation to sinus rhythm and appeared atria-selective as no QTc prolonging effect was observed post administration. Thus, SK channel inhibition may possess antiarrhythmic potential. However, NS8593 caused convulsions and is therefore excluded as an antiarrhythmic drug in its present form.

Resume

I dette speciale undersøges to lægemidlers antiarytmiske potentiale i kardiologi hos hest ud fra målinger af QT-intervallet på elektrokardiogrammet. Specialet er opdelt i to dele: Part I udgør det teoretiske grundlag, mens Part II beskriver et eksperimentelt studie.

Part I – Der gives en gennemgang af hjertets elektrofysiologi med fokus på principper for iongrundlaget, der ligger til grund for hjertets aktionspotentiale såvel som impulsoverledningen i hjertet. Desuden præsenteres sammenhængen mellem forskellige faser i hjertets aktionspotentiale og overfladeelektrokardiogrammet med særlig fokus på QT-intervallet. Endelig gives en gennemgang af atrieflimren hos heste, herunder mekanisme, klassificering og behandling af denne arytmi.

Aktuelle muligheder for håndtering af atrieflimren i heste er begrænset af moderat effektivitet og betydelige bivirkninger, herunder forlængelse af QT-intervallet. Forlængelse af QT-intervallet er blevet forbundet med livstruende ventrikulære arytmier. I forsøg på at undgå ventrikulære arytmier er der øget fokus på atrie-selektivitet. SK kanaler er for nyligt fundet udtrykt særligt i atrierne og inhibering af SK kanaler er blevet påvist at forhindre og behandle atrieflimren i kaniner, marsvin og rotter uden at pårvirke QT-intervallet. SK kanal inhibering er derfor en lovende ny terapeutisk mulighed i behandlingen af atrieflimren. Inhibering af SK kanaler i behandlingen af atrieflimren er dog aldrig blevet undersøgt hos heste. Formålet med dette speciale har derfor været at undersøge det antiarytmiske potentiale for en ny SK negativ modulator, NS8593, samt flekainid acetat, en velkendt natrium-kanal blokker, i behandlingen af atrieflimren hos heste.

Part II - **Materialer og metode:** Seks klinisk raske heste indgik først i en stående procedure. Efter en udvaskningsperiode på 2-11 dage indgik hestene i en procedure i anæstesi. *Stående procedure:* Hestene blev tildelt 2 mg/kg flekainid IV. *Procedure i anæstesi:* To heste blev tildelt 2 mg/kg flekainid IV, mens fire heste blev tildelt 5 mg/kg NS8593 IV. Elektrokardiogram blev registreret under sinusrytme og under elektrisk stimulering før og efter administration af det pågældende antiarytmiske lægemiddel. QTc-intervaller blev målt ud fra et elektrokardiogram før, under og efter infusion. **Resultater:** *Stående procedure:* Flekainid var veltolereret af alle heste. Fire heste, der blev tildelt flekainid i atrieflimren, konverterede til sinusrytme med et gennemsnit på 4,77 ± 1,76

minutter. En signifikant forlængelse (P <0,05) af QTc blev observeret 15, 20 og 25 minutter efter tildeling af flekainid. Samtidig var QRS signifikant forlænget (P <0,05) 10, 15, 20 og 25 minutter efter flekainid infusion. JTc intervallet var forlænget 15, 20 og 25 minutter efter flekainid blev tildelt. Ligeledes blev der observeret in stigning i HR 15, 20 og 25 minutter efter tildeling af flekainid. *Procedure i anæstesi:* Kramper blev observeret hos tre ud af fire heste, der blev tildelt NS8593. En ud af to heste, der blev tildelt flekainid i atrieflimren, konverterede efter 14.08 minutter. Alle heste, der fik NS8593 i atrieflimren, konverterede til sinusrytme med et gennemsnit på 10,22 ±1,87 minutter. Der var ingen signifikant (P>0,05) QTc forlængelse efter tildeling af NS8593. En stigning i HR blev observeret 20, 25 og 30 minutter efter tildeling af NS8593. **Konklusion:** Flekainid var veltolereret af alle heste. Den observerede QTc forlængelse var primært forårsaget af en QRS bredde forøgelse. Forlængelsen i JTc ved højere HR var sandsynligvis forårsaget af den anvendte metode for korrektion af QT intervallet. Ud fra disse resultater er flekainid, i en dosis af 2 mg/kg, et sikkert og effektivt antiarytmikum til behandling af akut atrieflimren hos heste. NS8593 konverterede alle heste i atrieflimren uden påvirkning af QTc intervallet og synes derfor at være atrie-selektiv. Ud fra disse resultater kan det derfor konkluderes, at SK kanal inhibering synes at have antiarytmisk potentiale. NS8593 forårsagede dog kramper og er derfor ikke anvendeligt som antiarytmisk lægemiddel i dets nuværende kemiske form.

Contents

1. Introduction

1.1 Background

The QT interval on the electrocardiogram has gained clinical importance because prolongation of this interval has been associated with life-threatening cardiac arrhythmias including ventricular torsades de pointes tachycardia and sudden death in both humans and animals (Roden et al., 1986, Reef et al., 1995). Multiple factors have been implicated in causing QT prolongation and among these antiarrhythmic drugs have gained special attention (Al-Khatib et al., 2003). Cardiac arrhythmias including atrial fibrillation have been treated traditionally with antiarrhythmic drugs that alter cardiac electrical properties (Workman et al., 2011). However, existing drugs are not specific for atrial electrical activity and may possess profound proarrhythmic effects on ventricular electrophysiology. By extending not only the atrial repolarization phase but also the ventricular repolarization phase these antiarrhythmic medications can prolong the QT interval, and thus, cause an increased risk of ventricular proarrhythmia (Nattel, 2002).

The antiarrhythmic drug, quinidine, has been reported to be the drug of choice for treating atrial fibrillation in horses (Deem and Fregin, 1982, Bertone and Wingfield, 1987, Reef et al., 1988, Muir et al., 1990, Reef et al., 1995). However, this drug has been reported to have both non-cardiac and cardiac side effects, including ventricular tachycardia and sudden death (Morris and Fregin, 1982, Reef et al., 1995). Therefore, pharmaceutical alternatives to quinidine, with less side effects and similar efficacy are desirable. Flecainide has been found to be well tolerated in horses and has been reported to be effective in restoring sinus rhythm in horses with acute atrial fibrillation (Ohmura et al., 2000, Ohmura et al., 2001). However, more recent data report that flecainide has limited potential in the treatment of naturally-occurring chronic atrial fibrillation in horses, and may induce potentially dangerous arrhythmias (van Loon et al., 2004, Birettoni et al., 2007). More recently, the antiarrhythmic drug, amiodarone, has been described in horses suffering from chronic atrial fibrillation (De Clercq et al., 2006, de Clercq et al., 2007b). Although this drug has some promising results for treatment of naturally-occurring atrial fibrillation and ventricular arrhythmia in the horse, severe side effects including diarrhea have been reported (De Clercq et al., 2006, de Clercq et al., 2007a, de Clercq et al., 2007b).

Current options for management of atrial fibrillation in horses are limited by moderate efficacy and significant associated adverse effects, including life-threatening ventricular proarrhythmia. Many

existing antiarrhythmic drugs affect ion channels in both atrial and ventricular tissue, and it is believed that their lack of selectivity may lead to an increased risk of possibly fatal ventricular arrhythmias (Diness et al., 2011). Therefore, there is a need for more specific and thus, more safe and efficacious drugs for treatment of atrial fibrillation. Ongoing drug development has therefore an increased focus on targeting ion channels specifically expressed in the atria (Xu et al., 2003). Atrial-selectivity, in an attempt to avoid ventricular proarrhythmia, may be achieved by targeting ion channels located in the atria and not in the ventricles (Ravens, 2010). A recently discovered atrial-selective target for atrial fibrillation is the calcium-activated potassium current, mediated by the small-conductance calcium-activated potassium (SK) channels (Özgen et al., 2007, Li et al., 2009). It has recently been demonstrated that inhibition of SK channels prolongs the atrial effective refractory period without affecting the QT interval. In addition, SK channel inhibition also prevents and terminates atrial fibrillation *ex vivo* an *in vivo* in rabbits, guinea pigs and rats, thus offering a promising new therapeutic opportunity in the treatment of atrial fibrillation (Diness et al., 2010). The amount of literature on the subject is however limited and SK channel inhibition as a target in the treatment of atrial fibrillation has so far never been investigated in the equine heart. This brought forth the motive of this thesis.

1.2 Aim of study

The purpose of this study was to investigate the efficacy and safety of the SK negative modulator, NS8593, as well as flecainide acetate, a class 1c antiarrhythmic drug, for treating equine atrial fibrillation. More specifically, the aim of the present study was to assess the effect of NS8593 and flecainide on the QT interval and thereby evaluate the antiarrhythmic potential of the two drugs in equine cardiology.

Part I - Theory

Prolongation of the QT interval on the surface electrocardiogram reflects prolonged repolarization of the ventricular action potential. Consequently, to understand the causal relationship between QT interval prolongation and induction of ventricular arrhythmias in horses, it is necessary to understand equine cardiac electrophysiology. Thus, the electrophysiology focusing on principles of ionic basis of the cardiac action potential as well as impulse conduction within the heart is reviewed in the theoretical part of this thesis. Furthermore, correlation between phases of the cardiac action potential and the surface electrocardiogram with special focus on the QT interval is presented. Finally, the following theoretical part of this thesis will provide an overview of atrial fibrillation in horses. Knowledge of this arrhythmia is central to an understanding of the second part of the thesis, as a pacing-induced acute model for atrial fibrillation is used in the experimental study of the thesis to evaluate drug effect on the QT interval.

2. Principles of equine cardiac electrophysiology

2.1 The cardiac action potential

Proper contraction and thereby pumping of the heart is controlled by electrical signals recognized as cardiac impulses or cardiac action potentials that originate from pacemaker cells in the right atrium. The cardiac action potential is mediated by changes in the ion conductance across the cell surface membrane. In the heart, these changes in conductance are primarily mediated by voltage gated ion channels, conducting sodium, calcium and potassium ions (Nerbonne and Kass, 2005). The resting myocardial cell (cardiomyocyte) has a high intracellular concentration of potassium and low levels of sodium and calcium resulting in an intracellular negative charge compared to the outside environment (Reed et al., 2010). Upon appropriate stimulation from a neighbor cardiomyocyte ion channels are activated and inactivated in a sequential way conducting depolarizing inward (sodium and calcium) and repolarizing outward (potassium) currents (Nerbonne and Kass, 2005). This movement of ions across the cell membrane results in changes in the membrane potential from about -90 mV to +20 mV (depolarization), and finally back to -90 mV (repolarization) (Marr and Bowen, 2010). The morphology of the cardiac action potential can be divided into five different phases, phase 0-4 (Reed et al., 2010). A summarized description of ionic currents involved in the different phases is given in figure 1.

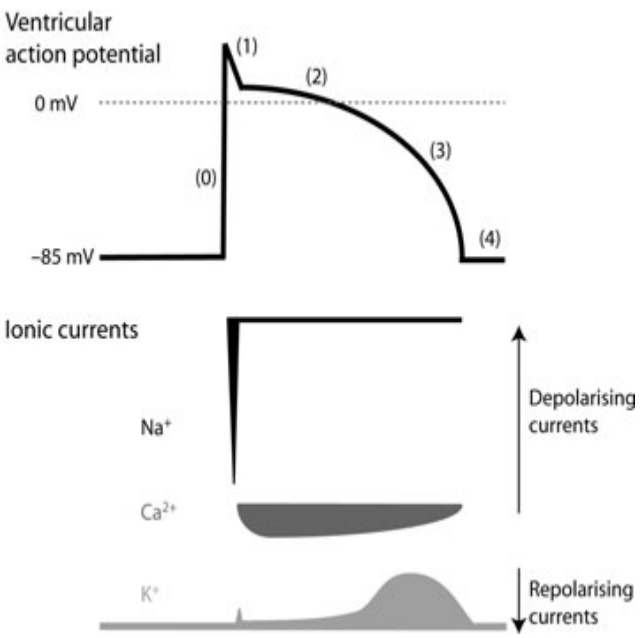

Figure 1 The relative balance between depolarizing currents, beings sodium and calcium, and repolarizing potassium currents shapes the cardiac action potential. The figure is modified from Tfelt-Hansen *et* al. (2009).

2.1.1 Depolarization

The ion current responsible for depolarizing the cardiac membrane in the atrial and ventricular cardiac cells is the sodium current (Tfelt-Hansen et al., 2010). Activation of voltage-gated sodium channels leads to a very fast depolarization of the cardiomyocyte (phase 0) (Jespersen, 2011). When a cardiomyocyte reaches the threshold at approximately -55 mV, as a result of depolarization of adjacent cells or spontaneously in pacemaker cells, voltage-gated sodium channels open (Nerbonne and Kass, 2005). This leads to a massive sodium influx that rapidly changes the membrane potential to about +20 mV (Marr and Bowen, 2010). Compared to the action potential of conduction pathway cells and myocardial cells, the sinoatrial and atrioventricular nodal cells have a slow depolarization phase. This slower phase occurs because the sinoatrial and the atrioventricular nodes mainly are dependent on slow calcium channels and lack rapid sodium channels (Nerbonne and Kass, 2005).

2.1.2 Repolarization

The initial fast depolarization of the cell membrane is followed by a transient repolarization (phase 1) (Grunnet, 2010). During this phase sodium channels are rapidly inactivated, resulting in an almost complete block of the inward sodium current. At the same time as the sodium channels starts

to inactivate, fast transient outward potassium channels briefly opens, giving an outward repolarizing current of potassium ions. This, together with the slower opening of calcium channels results in a partial repolarization (Jespersen, 2011). A long-lasting plateau phase (phase 2) follows the transient repolarization. The plateau phase is mainly the result of an influx of calcium. Voltage-gated calcium channels activated by depolarization have been slowly opening during phase 1. When the channels open calcium enters the cell and triggers a calcium-dependent calcium release from intracellular stores resulting in myocardial contraction (Bers, 2002). The combination of inward calcium and outward potassium currents nearly outbalancing each other during the plateau phase prolongs the action potential. The ionic current therefore determines the refractory period (Nattel, 2002). The slowly inactivation of the calcium channels together with the activation of different potassium channels resulting in a series of potassium currents out of the cell terminates the plateau phase (phase 3) (Grunnet, 2010). Activation of different types of potassium channels returns the cell to its diastolic resting membrane potential and the cardiac cell regains excitability (phase 4) (Jespersen, 2011).

2.1.3 The ionic channels and currents

Propagation and rapid depolarization (phase 0) of the cardiac action potential is mediated by an inward sodium current (I_{Na}). The voltage-gated sodium (Na_v) channel is responsible for conducting I_{Na} (Grunnet, 2010). Partial repolarization (phase 1) reflects Na_v channel inactivation and activation of the fast transient outward potassium current ($I_{To,\ f}$). Membrane depolarization also activates voltage-gated calcium (Ca_v) channels and the influx of the calcium current (I_{Ca}) through the Ca_v channels during the plateau (phase 2) (Nerbonne and Kass, 2005). The driving force for potassium efflux is high during the plateau phase of the action potential, and as the Ca_v channels inactivate, the outward potassium currents predominate resulting in repolarization (phase 3) (Nerbonne and Kass, 2005). In contrast to I_{Na} and I_{Ca}, however, there are several potassium currents involved in the repolarization of the cardiac myocytes, and the greatest diversity is among currents conducted through the voltage-gated potassium (K_v) channel (Nerbonne and Kass, 2005). The ultra rapid potassium current (I_{Kur}) is expressed in the atria. As $I_{To,\ f.}$, I_{Kur} is a fast activating current influencing the membrane potential in the early part of the action potential (Phase 1) (Jespersen, 2011). The rapid and slow delayed rectifier potassium currents (I_{Kr} and I_{Ks}) are, together with the inward rectifier current (I_{K1}), the primary currents responsible for repolarizing the cardiomyocyte

membranes in the final part of the action potential and thereby terminating it (Phase 3) (Jespersen, 2011). I_{Kr} is conducted through the ERG1 channel, a K_v channel. The unique features of the ERG1 channel make it pivotal in cardiac repolarization. Upon depolarization the ERG1 channels open but inactivate very fast. This means that the ERG1 channel conducts minor potassium current during the initial depolarization and the plateau phase. However, when the membrane potential moves towards a more repolarizing potential the ERG1 channels are released from inactivation. As ERG1 channels only slowly progress into a closed state a relative large potassium current is conducted and the membrane potential is accelerated towards the resting membrane potential (Jespersen, 2011). I_{K1} is conducted through the non-voltage-gated inward rectifier potassium (K_{ir}) channel and is the current primarily responsible for setting the resting membrane potential (phase 4) (Dhamoon and Jalife, 2005) (figure 2).

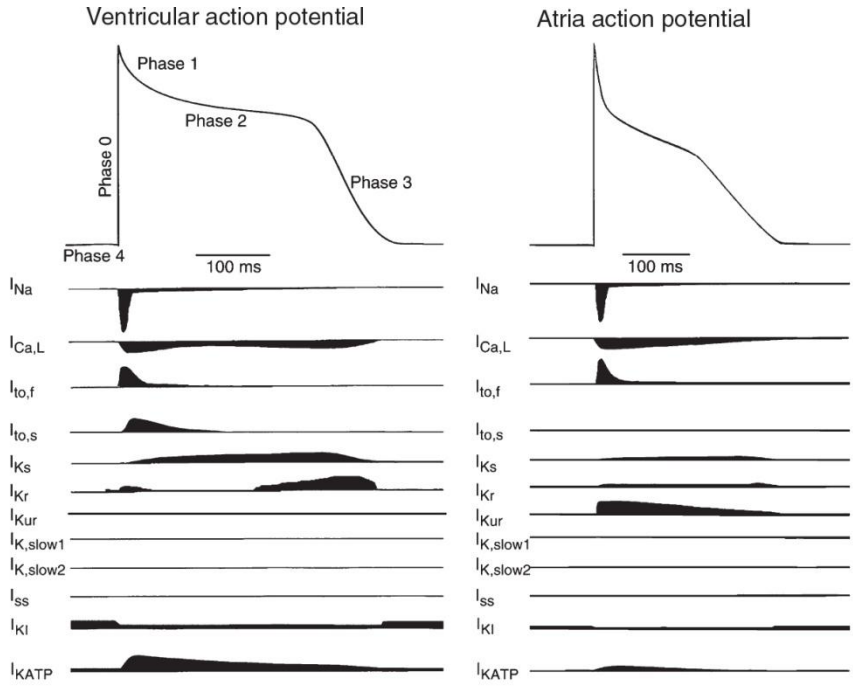

Figure 2 Ionic currents contributing to the action potential in ventricular (left) and atrial (right) cardiomyocytes. The time- and voltage-dependent properties of the inward sodium (I_{Na}) and calcium (I_{ca}) currents expressed in atrial and ventricular myocytes are similar. In contrast, there are multiple types of potassium currents, particularly potassium currents conducted through the voltage-gated potassium (K_v) channel, contributing to atrial and ventricular action potential repolarization. The relative contribution from the individual ionic currents is demonstrated by black shading. The depicted ion currents will not be representative of all conditions. For example, the contribution from K_{ATP} channels is very minor in situations with a normal metabolic state of the cardiomyocytes. Modified from Nerbonne and Kass (2005).

2.1.4 Refractoriness and action potential progression

When sodium channels close after the peak of an action potential they become inactivated (Tfelt-Hansen et al., 2010). While the sodium channels are inactivated the cell is resistant to the formation of a new action potential. This period is known as the effective refractory period (Marr and Bowen, 2010). Because sodium channel inactivation lasts until the membrane potential is restored to its resting level, the refractory period corresponds to the width of the action potential (Cunningham, 2002). However, during the end of phase 3 and phase 4 the cell can be excited by a large current. This period is known as the relatively refractory period (Marr and Bowen, 2010). The long refractory period in cardiac muscle guarantees a period of relaxation and cardiac refilling between contractions (Cunningham, 2002). Recovery of sodium channels from inactivation is faster and more complete at more negative voltage (Ravens, 2010). This implies a slower recovery of sodium channels in the atria as the resting membrane potential is more positive in the atria compared to the ventricles (Tfelt-Hansen et al., 2010).

The cardiomyocytes are electrically coupled to each other through gap junctions located at the intercalated discs. Gap junctions are specialized intercellular connections allowing various molecules and ions to pass freely between cells (Jespersen, 2011). When an action potential depolarizes the membrane of one cardiomyocyte, the positive ions flow through the gap junctions and into the neighbouring cell. This ionic current depolarizes the neighbouring cell to threshold for the formation of an action potential (Cunningham, 2002). Thus, the myocardium is termed a functional syncytium as only minor conduction velocity slowing is observed when the electrical impulse passes from one myocyte to another (Jansen et al., 2010).

2.2 Normal impulse propagation and conduction

The prerequisite for proper contraction and thereby cardiac function is that the electrical signals are highly coordinated. The electrical impulse is initiated in the pacemaker cells in the sinoatrial node (SAN) located in the junction of the cranial vena cava and the right atrium (Miller and Bonagura, 1985). The impulse then propagates through the atria, thereby initiating muscular contraction of the atria and the appearance of a P wave on the electrocardiogram, indicating atrial depolarization (Perry and Illsley, 1986). When the electrical impulse reaches the atrioventricular node (AVN) at the junction of the right atria and right ventricle the conduction is slowed, thereby securing atrial contraction previous to ventricular contraction (Miller and Bonagura, 1985). This allows ventricular

filling to finish before the depolarization progresses to the ventricular cardiomyocytes (Cunningham, 2002). The slow conduction of the impulse through the AVN does not result in a deflection on the electrocardiogram and is represented as the P-R interval (Verheyen et al., 2010). The electrical impulse is then rapidly spread to the ventricles through a specialized conduction system formed by the Hiss Bundle and the Purkinje fibers, resulting in a coordinated depolarization of the ventricles and thereby a synchronized muscle contraction (Perry and Illsley, 1986). After the depolarization and the plateau phase the myocardium repolarizes and the contraction ceases allowing ventricular refilling (Cunningham, 2002). Depolarization of the ventricles produces the QRS complex on the electrocardiogram (Verheyen et al., 2010). The QRS complex is the name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The Q, R, and S waves occur in rapid succession and reflect a single event, and thus are usually considered together. A Q wave is any downward deflection after the P wave. An R wave follows as an upward deflection, and the S wave is any downward deflection after the R wave. Not every QRS complex contains a Q wave, an R wave, and an S wave, and an rS or rSr' morphology is more common in horses (Verheyen et al., 2010). The T wave on the electrocardiogram represents ventricular repolarization (Verheyen et al., 2010). Therefore, the QT interval is an indirect measurement of the ventricular repolarization and is measured from the beginning of the QRS complex to the end of the T wave (Al-Khatib et al., 2003). The correlation between electrical activity in the myocardium and surface electrocardiogram is shown in figure 3.

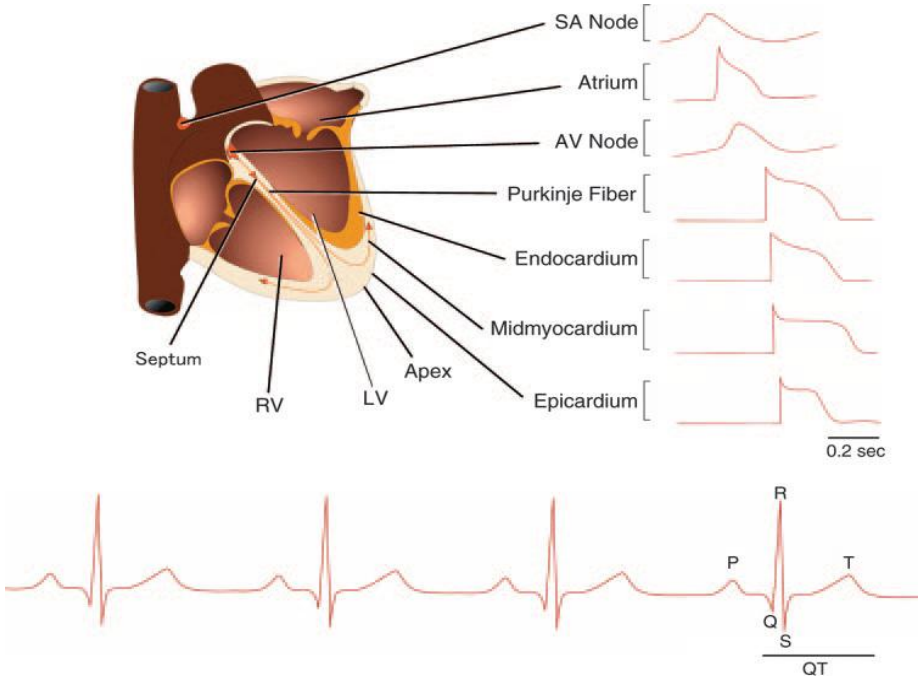

Figure 3 The electrical activity in the myocardium. *Top*: schematic drawing of the heart with illustrations of representative action potentials, which can be recorded in the different locations of the heart. *Bottom*: schematic drawing of a surface electrocardiogram; three sequential beats are displayed. The surface electrocardiogram reflects the relative muscle mass being either depolarized or repolarized. Hence, the P-wave reflects atrial depolarization, the QRS complex ventricular depolarization, and the T-wave ventricular repolarization. Adapted from (Nerbonne & Kass 2005).

The following section will focus on the QT interval as prolongation of this interval is widely accepted as a biomarker for the potential of drug-induced lethal ventricular arrhythmias.

2.3 The QT interval

The QT interval on the electrocardiogram represents the cellular ventricular action potential and is the net result of coordinated function of various ionic currents as outlined previously in this thesis. The sodium and calcium inward currents are primarily responsible for the action potential upstroke and depolarization, whereas outward potassium currents in combination with a reduction in depolarizing currents are predominantly responsible for cardiomyocyte repolarization (Nattel, 2002). Alterations in inward and outward ionic currents can therefore dramatically change the duration of the plateau phase and thereby the action potential duration (Nattel, 2002). Increases in depolarization currents and/or decreases in repolarizing currents due to malfunction of ion channels will prolong the action potential duration. An intracellular surplus of positive ions in the ventricles

prolongs the ventricular action potential and thereby the QT interval (Viskin, 1999). The repolarization phase of the action potential is especially important in QT interval prolongation, resulting predominantly from attenuated outward movement of potassium ions (Patel et al., 2011).
The long QT syndrome (LQTS) is characterized by a prolonged interval between the Q and the T wave on the electrocardiogram and is associated with increased risk of sudden death (Tfelt-Hansen et al., 2010). As the QT interval gets longer, the risk of the next cardiac impulse to occur and strike at the relative refractory period increases. The relative refractory period occurs from the peak of the T wave to the latter portion of the T wave. If any new impulse occurs during this period, the cardiac rhythm can develop a tachyarrhythmia such as ventricular tachycardia deteriorating to ventricular fibrillation (Hutton, 2008). LQTS can be found in an inherited (congenital) as well as in an acquired form (Tfelt-Hansen et al., 2010). The acquired form of LQTS is more relevant to veterinary medicine and is often caused by pharmacological drugs (Finley et al., 2003). Over the past decade it has become apparent that class I antiarrhythmic drugs such as quinidine, procainamide and flecainide may prolong the QT interval and induce fatal ventricular arrhythmias (Finley et al., 2003). Proarrhythmia is one of the common adverse effects of class Ia antiarrhythmic drugs such as quinidine, because these drugs prolong the action potential duration by blocking not only sodium currents, but also potassium currents (Finley et al., 2003). Acquired LQTS is generally associated with drug-induced block of the ERG channel and inhibition of I_{Kr} (Yang et al., 2001). With I_{Kr} inhibition the risk of ventricular tachycardia and torsades de pointes increases (Yang and Roden, 1996). Traditionally, horses in atrial fibrillation are treated with class I antiarrhythmic drugs and therefore are at risk of developing drug-induced ventricular arrhythmias and torsades de pointes (Deem and Fregin, 1982, Bertone and Wingfield, 1987, Reef et al., 1988, Muir et al., 1990, Reef et al., 1995).

2.3.1 QT Dynamics

The QT interval is very heart rate dependent. Normally, the QT interval shortens when the heart rate fastens and prolongs at a slower heart rate (Luo et al., 2004). Thus, this adaption makes it difficult to find out whether a measured QT change is due to a drug repolarization effect or a function of a change in heart rate (Desai et al., 2003). Also, this connection between QT interval and heart rate makes it difficult to compare the QT interval recorded at different heart rates (Malik et al., 2002). Therefore, the QT interval is corrected for heart rate in humans using different formulas (Luo et al.,

2004). However, no QT correction formula for equine QT correction is available and some researchers have taken human correction methods into use (Schwarzwald et al., 2007). The QT interval also gradually adapts to changes in the RR interval, a phenomenon called QT lag (Larroude et al., 2006). In a variable rhythm such as atrial fibrillation, the influence of lag on the average QT interval becomes more important and a simple way to adjust for QT lag by pairing the QT interval with a weighted average of the preceding 5 RR intervals was introduced by Ehlert *et al*. (Ehlert et al., 1992). Larroude *et al*. also demonstrated that QT dynamics in atrial fibrillation can be measured more reliably if additional RR intervals are included in the QT calculation (Larroude et al., 2006).

This section has outlined cardiac electrophysiology focusing on principles of ionic basis of the cardiac action potential as well as impulse conduction within the heart. Further, correlation between phases of the cardiac action potential and the surface electrocardiogram with special focus on the QT interval has been reviewed. The following section of the theoretical part of this thesis will provide an overview of the mechanism, classification and management of atrial fibrillation in horses. As a pacing-induced acute model for atrial fibrillation is used in the experimental study of the thesis to evaluate drug effect on the QT interval an appreciation of this arrhythmia is central to the understanding of the second part of this thesis.

3. Atrial fibrillation in horses

Atrial fibrillation is a condition where the atria no longer contract in a coordinated manner and is definitively diagnosed by electrocardiography (Holmes, 1980, Blissitt, 1999). Electrocardiographic changes include irregular R-R intervals, an absence of P waves, and the presence of small irregular baseline fibrillation "f" waves (Bertone and Wingfield, 1987) (see figure 4). In comparison an electrocardiogram obtained from a horse in normal sinus rhythm shows regular R-R intervals and P waves (see figure 5).

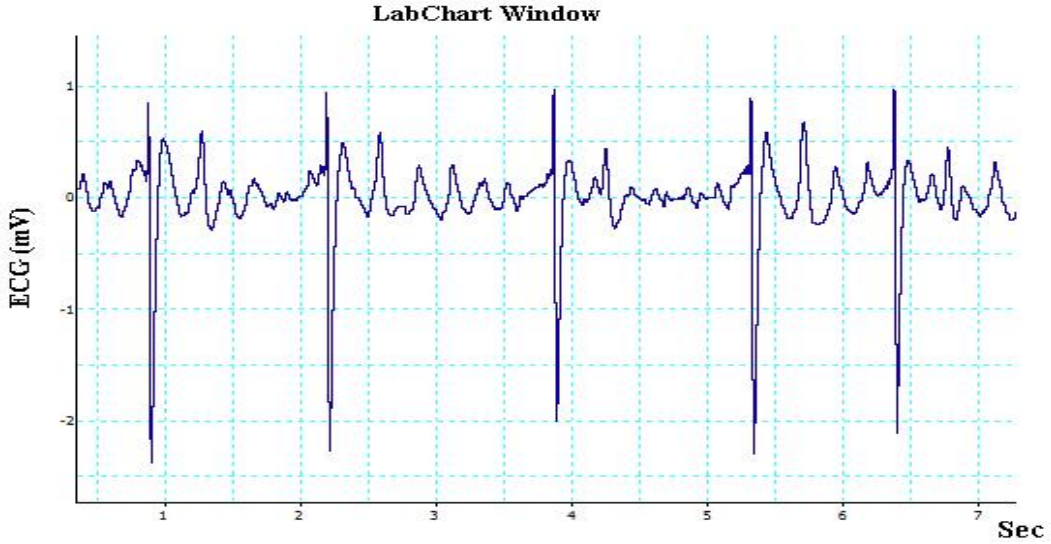

Figure 4 Base-apex ECG obtained from a horse with atrial fibrillation. Notice the irregular R-R intervals and fibrillation waves. ECG recording obtained during the study procedures.

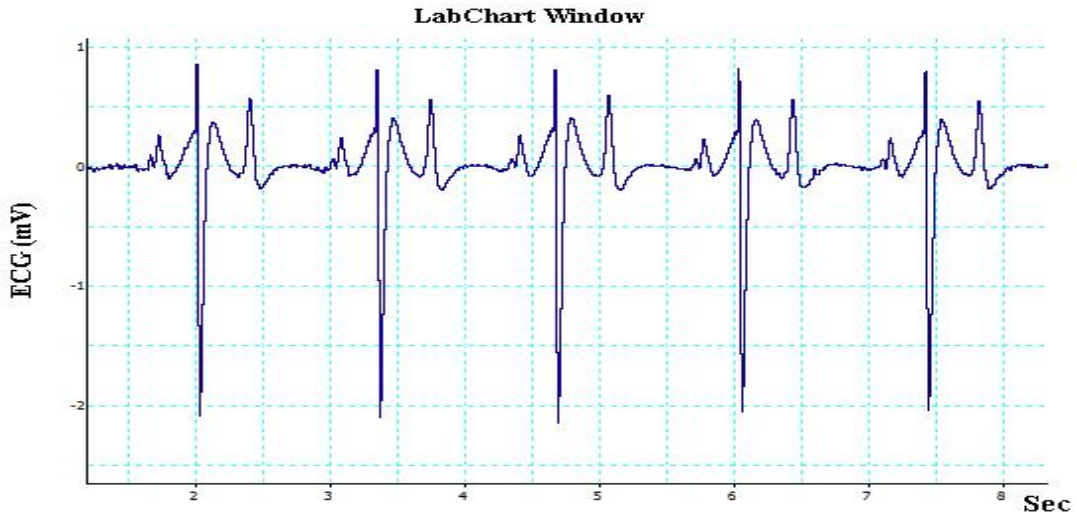

Figure 5 Modified base-apex ECG from a horse in sinus rhythm. ECG recording obtained during the study procedures.

Atrial fibrillation is considered the most clinically relevant arrhythmia causing poor performance in the athletic horse (Deem and Fregin, 1982, Holmes et al., 1986, Manohar and Smetzer, 1992, Hiraga and Kubo, 1999, Ohmura et al., 2003). Though atrial fibrillation is often an incidental finding during routine examination, particularly in horses that do not perform at higher levels, the estimated minimum frequency (123 episodes of atrial fibrillation following 404,090 race starts) of atrial fibrillation in Japanese racehorses is reported to be 0.03% with an estimated minimum prevalence (115 horses with atrial fibrillation among 39,302 racehorses) of atrial fibrillation among Japanese racehorses being 0.29% (Ohmura et al., 2003). A similar frequency of atrial fibrillation among racehorses (0.049%) has been reported in the UK (Holmes et al., 1986). No gender predisposition seems to appear but atrial fibrillation is reported to be more prevalent in racehorses more than 4 years of age compared to younger horses (Deem and Fregin, 1982, Ohmura et al., 2003) Many horses with atrial fibrillation perform well at rest and during mild exercise but are intolerant to strenuous exercise because of loss of atrial pump function. As atrial mechanical function contributes to ventricular preload and stroke volume, normal atrial function is crucial for maintaining adequate cardiac output in athletes (Holmes et al., 1986).

In contrast to humans, atrial fibrillation in horses frequently occurs without any detectable cardiac disease, in which it is classified as “lone” atrial fibrillation (Deem and Fregin, 1982, Reef et al., 1988). These horses are good candidates for medical conversion to sinus rhythm. In contrast, successful cardioversion is less likely in horses with an underlying cardiac disease and recurrence of atrial fibrillation following successful treatment is more common (Reef et al., 1988).

3.1 The mechanism of atrial fibrillation

Atrial fibrillation is thought to be associated with a phenomenon of re-entry or circus movement (Marr and Bowen, 2010). Re-entry is rapid circuitous myocardial activation by an action potential wavefront as it continuously circulates a region of conduction block, re-exciting previously refractory tissue. The region of conduction block may be functional, i.e., an area of refractory tissue, or anatomical/structural, e.g., a coronary vessel or a myocardial lesion; giving rise to functional and anatomical/structural re-entry, respectively (Workman et al., 2011). Re-entry occurs when an area of myocardium develops slow conduction of action potentials and the ability to conduct action potentials in only one direction (unidirectional block). If a portion of myocardium has slow conduction it can be refractory to an initial stimulus, but has become able to be

depolarized by the time an impulse is conducted to it via another route (Marr and Bowen, 2010) (figure 6).

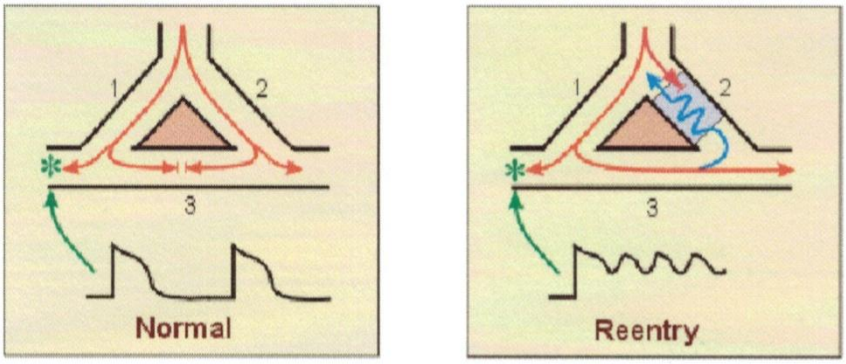

Figure 6 Normal and re-entry propagation of electrical signals. In a normal situation the electrical signal spreads around a non-conducting region with equal velocity (1 and 2). The two signals will propagate in the left and right direction with equal velocity. When colliding in point 3 they will therefore encounter refractory tissue and die out. The right part of the figure demonstrates a re-entry scenario giving rise to an arrhythmogenic event. A unidirectional block is presented by the grey area. When the signal branches off it only has the possibility of propagating in one direction as the signal moving towards the grey area will die out due to the unidirectional block. The signal travelling through the conducting pathway (branch 1) does however have the potential to continue propagation through point 3 and thereby re-enter via the grey area in point 2 as a consequence of the block being unidirectional. If the conducting signal re-enters point 1 at a time period where the tissue is no longer refractory this will result in excitation at point 1 and self-sustained wave propagation can be initiated. The green star denotes a recording electrode recording normal or arrhythmogenic action potentials. Adapted from Grunnet (2010).

The hypothesis that atrial fibrillation is a result of multiple re-entrant waves has been the dominant theory for many years (Moe and Abildskov, 1959, Nattel, 2002). The theory was substantiated by the work of Allessie *et al*., who experimentally demonstrated that re-entry could be obtained without any anatomical obstacles when premature extra stimuli were applied to rabbit left atria (Allessie et al., 1976, Allessie et al., 1977). These observations were used to develop the "leading circle" model for functional re-entry. According to the leading circle theory, the maximal number of simultaneous waves depends on the refractory period, mass, and conduction velocity in the atria (Allessie et al., 1977). A large number of waves are required for atrial fibrillation to be self-sustained (Moe and Abildskov, 1959). The more waves present in the atria at the same time, the smaller is the statistical probability that all atrial cardiac cells are either simultaneously refractory or excitable and the smaller is the chance for termination of atrial fibrillation (Moe and Abildskov,

1959). A large atrial mass can contain more waves (Moore and Spear, 1987). In addition, the atria can include a higher number of waves when the wavelength in decreased (Nattel, 2002). The wavelength is the distance travelled by the electrical impulse, which is a product of the conduction velocity and the refractory period. Therefore, decreased conduction velocity or decreased refractory period will shorten the wavelength (Nattel, 2002) (figure 7).

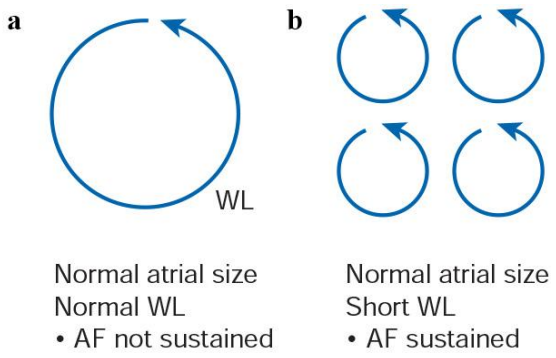

Figure 7 The principle of leading circle re-entry. **a.** In normal tissue WLs are sufficiently long to allow only few re-entry waves. **b**. When recalling that WLs are the product of refractory period (RP) multiplied by conduction velocity (CV) it becomes clear that both decreased RP or decreased CV will shorten WLs. The more WLs that can be encompassed in the tissue the higher is the likelihood of re-entry-based arrhythmias. A shortening of WLs will thereby increase the risk of re-entry-based arrhythmias. WL: wavelength, AF: atrial fibrillation. Adapted from Nattel (2002).

Horses are particularly predisposed to the development of atrial fibrillation in normal atrial tissue because the equine atria are large and they have a high vagal tone (Bertone and Wingfield, 1987). Vagal stimulation is a strong promoter of atrial fibrillation in part because it reduces the atrial effective refractory period, which decreases the electrical wavelength. It has also been demonstrated that vagal stimulation shortens atrial refractoriness non-uniformly, which accentuates dispersion of refractoriness and facilitates atrial fibrillation (Alessi et al., 1958, Rensma et al., 1988). Both the shortening of the refractory period and the inhomogeneity of refractoriness are arrhythmogenic because a premature impulse generated during a period of vagal stimulation will encounter areas in varying states of excitability. Some areas are in the refractory state and are not able to propagate activation, while other areas have recovered from the refractory state and will propagate excitation. This gives the chance for the re-entry mechanism described above to develop (Abildskov et al., 1971).

During the last 50 years the leading circle model has been the main mechanism to explain atrial fibrillation in different animal models (Jalife, 2003). However, this model does not explain why blockers of sodium channels are effective in terminating arrhythmias as described later. According to the leading circle, sodium channel blockers should promote atrial fibrillation by decreasing the conduction velocity and consequently decreasing the wavelength (Nattel, 2002). A never, more complex, model for explaining cardiac re-entry is the "spiral wave" model for re-entry (Davidenko et al., 1992) (figure 8).

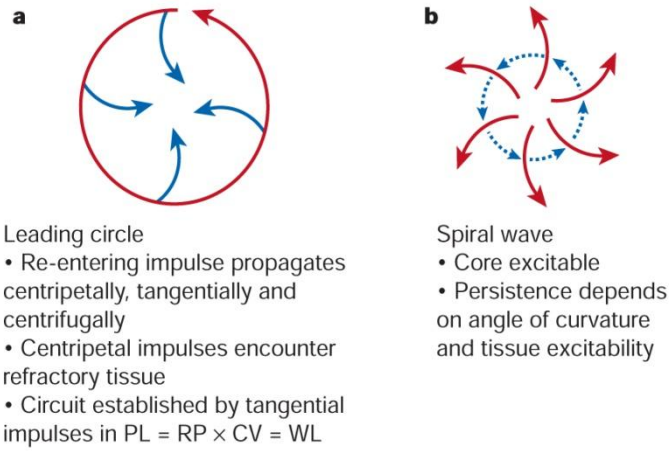

Figure 8 Models of re-entry. **a**; Mechanism of functional re-entry in the leading circle model**. b**; spiral wave model of re-entry. PL: Path length, RP: refractory period, CV: conduction velocity, WL: wavelength. Adapted from Nattel (2002).

According to this model, a spiral wave continuously rotates around a central core of constant size. In contrast to the leading circle model, where the central cores of re-entry circuits are constantly refractory because of continual excitation, the core of the spiral wave is non-activated and excitable. An excitable core with short refractoriness supports the angle of a curved spiral wave. According to the spiral wave model, a reduction of the sodium current leads to an increased meandering of the core as well as increased core size and decreased curvature, all of which can be antiarrhythmic (Comtois et al., 2005).

The spiral wave model explains the antiarrhythmic effect of potassium blockade by increased meandering as well as the increased refractory period increases the likelihood for breakup of the

spiral wave. Thus, in addition to explaining how potassium blockade is antiarrhythmic, the spiral wave also explains the antiarrhythmic effects of blockers of sodium channels (Comtois et al., 2005).

3.2 Classification of atrial fibrillation

Classification of atrial fibrillation subtypes can be achieved on the basis of the duration of the episodes and ease by which episodes terminate (Allessie et al., 2001). Paroxysmal atrial fibrillation is often associated with a single episode of poor performance, with the horse often decelerating suddenly during a race (Holmes et al., 1986, Hiraga and Kubo, 1999). Paroxysmal atrial fibrillation terminates spontaneously, with episodes usually lasting less than 24 hours and up to 7 days (Patel et al., 2011). Persistent atrial fibrillation last more than 7 days and can only be terminated with treatment, whereas permanent atrial fibrillation describes continuous atrial fibrillation that cannot be terminated despite treatment (Patel et al., 2011).

Atrial fibrillation is understood to begin as the paroxysmal form which then can progress to persistent atrial fibrillation. Further, atrial fibrillation can be maintained and eventually becomes permanent (Nattel, 2011). The progression from paroxysmal atrial fibrillation to persistent and then permanent atrial fibrillation involves both electrophysiological and structural remodelling in the atria (Van Wagoner and Nerbonne, 2000). The underlying electrophysiological mechanisms are related to altered expression and regulation of ion channels. As a consequence, multiple cellular functions are altered including stability of the membrane potential. Structural changes in atrial fibrillation includes increased amounts of fibrotic tissue, atrial dilation and hypertrophy (Van Wagoner and Nerbonne, 2000). Wijffels *et al.* previously demonstrated that repeated induction of atrial fibrillation in goats result in long-term changes in electrophysiological and structural properties in the atria which are thought to contribute to the tendency of atrial fibrillation to become persistent with longer duration (Wijffels et al., 1995). This phenomenon, that atrial fibrillation is self-perpetuating, has given rise to the expression “atrial fibrillation begets atrial fibrillation” (Wijffels et al., 1995). This is also known from the clinic, where horses with a recent onset of atrial fibrillation are more easily converted to sinus rhythm than horses with long standing atrial fibrillation (Reef et al., 1988). In addition, the recurrence rate increases with increased duration of atrial fibrillation (Allessie et al., 2001).

3.3 Management of atrial fibrillation in horses

The primary approach to atrial fibrillation has been to increase the refractory period. A long refractory period increases the chances that the circulating impulse encounters refractory tissue and subsequently terminates (Ravens, 2010). Traditionally, atrial fibrillation has been treated with drugs that increase the refractory period by altering the electrical properties of ion channels in the heart. Pharmacologically, these drugs have been classified on the basis of which ion channel they block (Vaughan Williams, 1984). Accordingly, drug classes I-IV block sodium channels, β-adrenergic receptors, potassium channels, and calcium channels respectively, whereas newer multichannel blockers such as amiodarone have been introduced later. Class I drugs are further subdivided into subclasses a, b and c, according to their effects on conduction velocity, action potential duration and effective refractory period (Vaughan Williams, 1984). There is a wide variety of antiarrhythmic drugs for treating atrial fibrillation but in horses only a few have been tested and introduced in the clinic and only a few of these drugs are discussed below.

3.2.1 Quinidine

Quinidine remains the drug of choice for traditional treatment of AF in horses (Deem and Fregin, 1982, Bertone and Wingfield, 1987, Reef et al., 1988, Muir et al., 1990, Reef et al., 1995). Quinidine is a class Ia antiarrhythmic drug. As mentioned above, the main recognized action of this drug is sodium channel blockade. This decreases the maximum upstroke (phase 0) velocity of the action potential and thereby reduces the conduction velocity (Ravens, 2010, Workman et al., 2011). Quinidine also blocks several potassium currents in addition to sodium channel blockade and is reported to be a potent I_{Kr} blocker (Yang et al., 2001). Potassium current inhibition may be expected to increase the atrial refractory period by increasing the action potential but inhibition of I_{Na} alone can also increase the atrial refractory period leading to extinction of re-entry waves (Workman et al., 2011). However, I_{Kr} block is associated with LQTS and torsades de pointes (Yang et al., 2001). Quinidine also has vagolytic properties and therefore antagonizes the vagally shortening of the refractory period. Thus, quinidine not only directly lengthens the refractory period but also acts indirectly to lengthen this parameter by its anticholinergic effect (Risberg and McGuirk, 2006). However, the anticholinergic effect of quinidine can enhance the atrioventricular nodal conduction. The resulting rapid ventricular response rate is a common reason for aborting therapy before

conversion to sinus rhythm, and is reported as the most common severe adverse effect of quinidine therapy in horses (Collatos, 1995).

Conversion to sinus rhythm carries a good prognosis if no significant underlying cardiac disease is present and horses commonly return to performance at their previous level (Reef et al., 1988). Atrial fibrillation in horses is usually treated by oral administration of quinidine sulfate. A dosage of 20 mg/kg or 22 mg/kg PO every 2 hours until therapeutic concentrations are achieved or signs of toxicity occur has been described (Deem and Fregin, 1982, Bertone and Wingfield, 1987, Reef et al., 1995, Blissitt, 1999). The antiarrhythmica requires administration through a nasogastric tube, as the drug is very bitter and acidic and may cause oral ulcerations if administered orally (Risberg and McGuirk, 2006). Intravenous administration of quinidine gluconate has also been described. However, this preparation, although more convenient, appears to be less effective when the arrhythmia is longstanding and it is frequently necessary to follow with oral administered quinidine sulfate before cardioversion takes place (Muir et al., 1990)

Treatment of atrial fibrillation with quinidine sulphate is effective in 85% of horses with atrial fibrillation of duration less than 2 months and without the presence of a detectable cardiac disease (Deem and Fregin, 1982, Reef et al., 1988). However, quinidine has the potential to cause adverse mild to severe cardiac and non-cardiac side effects, including hypotension, tachycardia, nasal mucosal edema, urticaria, severe colic and diarrhea (Morris and Fregin, 1982, Birettoni et al., 2007). Furthermore, proarrhythmic effects of quinidine can induce torsades de pointes and sudden death (Birettoni et al., 2007).

3.2.2 Flecainide

Based on reports of fewer adverse effects, flecainide is used as an alternative to quinidine for medical conversion of atrial fibrillation in horses (Ohmura et al., 2000, Ohmura et al., 2001). Flecainide is classified as a Vaughan Williams class Ic antiarrhythmic drug (Vaughan Williams, 1984). As a potent sodium blocker it mainly inhibits I_{Na}, and thereby significantly slows the upstroke velocity of the action potential in myocardial cells leading to an increase in wavelength of the re-entry waveform (Patel et al., 2011, Workman et al., 2011). Like other class I antiarrhythmic drugs flecainide also inhibits I_{Kr}. (Wang et al., 1996). Thus, the action of flecainide is characterized by marked prolongation of the duration of PR and QRS intervals and minimal changes in QT intervals (Roden and Woosley, 1986).

In humans, flecainide has been shown to be an effective antiarrhythmic agent for the acute termination of paroxysmal atrial and ventricular tachyarrhythmias and the efficacy in converting paroxysmal atrial fibrillation to sinus rhythm has been reported to be 90% when administered intravenously (Nathan et al., 1987). The efficacy of a single oral loading dose of flecainide for pharmacological cardioversion of recent onset of atrial fibrillation in humans was found to be 91% at 8 hours after drug administration (Capucci et al., 1992). Ohmura *et al.* investigated the use of intravenous flecainide for the treatment of experimentally-induced acute atrial fibrillation in horses and reported that flecainide was well tolerated and was effective in restoring sinus rhythm (Ohmura et al., 2000). However, more recent data report that flecainide administered intravenously has limited potential in the treatment of naturally-occuring chronic atrial fibrillation in horses and even induce potentially dangerous arrhythmias (van Loon et al., 2004, Birettoni et al., 2007). Risberg and McGuirk found that flecainide effectively converted a horse with naturally-occuring atrial fibrillation to normal sinus rhythm, but that the horse experienced similar adverse effects to those observed with quinidine (Risberg and McGuirk, 2006). Also, two cases of sudden death in horses given flecainide orally within 24 hours of unsuccessful attempts of conversion with quinidine sulphate has been reported (Robinson and Darien, 2008).

Horses are treated with 2 mg/kg flecainide acetate by intravenous infusion of 0.2 mg/kg/min. (van Loon et al., 2004) or by the oral route as described by Ohmura *et al*. (Ohmura et al., 2001).

3.2.3 Amiodarone

More recently, the use of amidarone, a class III antiarrhythmic drug, has been described in horses suffering from chronic atrial fibrillation (De Clercq et al., 2006, de Clercq et al., 2007b). In a study by De Clercq *et al.* six horses with chronic atrial fibrillation received 5 mg/kg/h of intravenous amidarone for 1 hour followed by 0.83 mg/kg/h for 23 hours and, subsequently, 1.9 mg/kg/h for 30 hours (De Clercq et al., 2006). With this protocol, four out of six horses successfully converted to sinus rhythm. In another study six horses with chronic atrial fibrillation were treated with an intravenous amiodarone protocol consisting of 2 phases with a loading dose followed by a maintenance infusion. Three out of six horses cardioverted successfully without side effects (de Clercq et al., 2007b). Although the drug has shown some promise in treating naturally-occurring atrial fibrillation and ventricular arrhythmia in the horse, side effects, including diarrhea, have been reported (De Clercq et al., 2006, de Clercq et al., 2007a, de Clercq et al., 2007b).

Amiodarone is predominantly a potassium channel blocker and is a potent blocker of I_{Kr}. However, although QT prolongation is regularly observed during amiodarone treatment, torsades de pointes is rare in humans (Mattioni et al., 1989). In addition to potassium channel blockade, amiodarone also blocks sodium and calcium channels, and has α- and β-antiadrenergic activity. Thus, amiodarone displays activity corresponding to all 4 Vaughan Williams classes, which may explain higher efficacy of the drug in maintaining sinus rhythm (Patel et al., 2011). The potential for non-cardiac side effects in horses is however reported to be a limiting factor of amiodarone treatment (de Clercq et al., 2007b).

3.2.4 Transvenous electrical cardioversion

As an alternative treatment of horses with chronic atrial fibrillation or horses that are drug intolerant, transvenous electrical cardioversion has been described (McGurrin et al., 2003, McGurrin et al., 2005b, van Loon et al., 2005, McGurrin et al., 2008, De Clercq et al., 2008a) Two cardioversion electrodes are inserted via the jugular vein in the standing horse. Positioning of the catheters in the right atrium is guided using echocardiography. After induction of anesthesia both catheters and a surface ECG are connected to a defibrillator. Cardioversion is started at 50 Joule and increased in a stepwise manner until cardioversion is achieved (McGurrin et al., 2005a, De Clercq et al., 2008a). In human medicine, electrical cardioversion is an established technique in addition to pharmacological cardioversion for the restoration of sinus rhythm, and transvenous electrical cardioversion has been reported to be of higher efficacy than transthoracic cardioversion (Levy et al., 1992). Though a success rate of 98% for transvenous electrical cardioversion in horses has been reported, the procedure is difficult in horses because it requires anesthesia, and is more invasive, time-consuming and expensive (McGurrin et al., 2005b). In addition, immediate recurrence of atrial fibrillation after successful electrical cardioversion is common (De Clercq et al., 2008a).

3.2.5 SK-negative modulator (NS8593)

Within the last few years, the existence of cardiac small conductance calcium-activated potassium (SK) channels has been documented and their functional role is gradually being investigated. Three subtypes of SK channels exist, and evidence indicates that SK2 channels are predominantly expressed in the atria of the human and mouse heart as compared with the ventricles (Xu et al., 2003). These channels may target cardiac disease in an atrial selective behavior, thereby lowering

the risk of ventricular proarrhythmic effects. The exact role of SK channels in the heart remains unknown, but they have been suggested to play an important role in atrial repolarization and fibrillation, making them interesting and possibly atrial-specific targets (Li et al., 2009, Özgen et al., 2007). Inhibition of SK channels may therefore constitute a promising new therapeutic target in the treatment of atrial fibrillation with a decreased risk of ventricular proarrhythmia (Nattel, 2009). A new class of selective SK channel inhibitors that do not block the channel pore but modulates all SK channels negatively by decreasing the sensitivity towards calcium has recently been found (Strøbæk et al., 2000, Strøbæk et al., 2006). NS8593 is an example of a compound from this structural class and it has shown to prolong the atrial effective refractory period and to prevent and revert atrial fibrillation induction without affecting the QT-interval in rabbits, guinea pigs and rats (Diness et al., 2010, Skibsbye et al., 2011). An intravenous application of 5 mg/kg of NS8593 is used for medical management of atrial fibrillation (Skibsbye et al., 2011).

The general mechanism, classification and management of atrial fibrillation in horses were outlined in this section. In the following part of this thesis a pacing-induced acute model for atrial fibrillation is used to evaluate drug effect on the QT interval.

Part II – Experimental study

4. Materials and methods

4.1 Horses

Six Standardbred trotters were included in the study. The group consisted of four geldings and two mares (age range 4-9 years; weight range 390-552 kg). The criterion for inclusion in the group was the absence of any recognized cardiovascular disease. All horses were considered healthy based on history, clinical examination, cardiac auscultation, 24-hours electrocardiogram, as well as a standard echocardiographic examination. The horses arrived at the hospital 7-15 days before the study and were trained 5-10 days to stand unsedated and relaxed in a stock (see figure 9). None of the horses received medication during the training days before the study. The study protocol was approved by The Danish Animal Experiments Inspectorate (study license number 2011/561-55).

4.2 Overall study design

The study consisted of two separate procedures. First the horses were enrolled in a standing transvenous procedure (conscious study). After a wash-out period of 2-11 days, the same horses were included in a transvenous procedure during anesthesia (unconscious study) (see figure 9).
Conscious study: None of the horses were sedated during this study. The horses received 2 mg/kg of the antiarrhythmic drug flecainide (Tambocor, 10 mg/ml) intravenously over 10 minutes. Unconscious study: Two horses were given 2 mg/kg of flecainide intravenously over 10 minutes, while four horses were given 5 mg/kg of the test drug NS8593 (NeuroSearch A/S, Ballerup, Denmark) intravenously over 10 minutes.

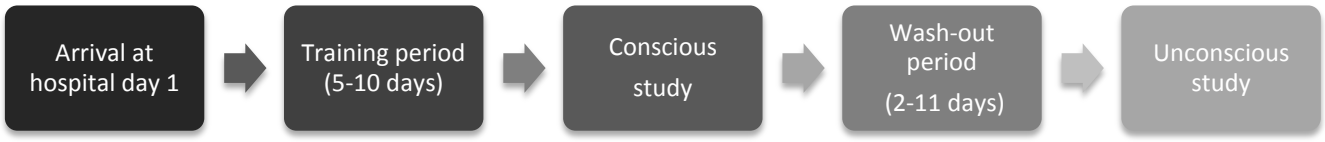

Figure 9 Study timeline.

4.2.1 Electrocardiography during the conscious procedure

4.2.1.1 Catheterization

Prior to catheterization the right and left jugular furrows were clipped and scrubbed with chlorhexidine soap until clean, followed by alcohol. 1-2 ml of lidocaine[1] was injected subcutaneously at the entry site of each catheter. An intravenous 12-gauge (12G) catheter was placed in the left jugular vein for drug administration, blood sampling, and routine access. Two 12G catheters were placed in the right jugular vein approximately 10 cm apart. A guidewire from the introducer catheter sheath[2] was placed in each catheter in the right jugular vein. The two 12G catheters were then removed so that only the two guidewires were placed in the vein. An 8F introducer catheter was placed in both the proximal and distal catheter sites with help from the guidewire. To be able to place the introducer catheters a 2-3 mm skin incision was made. The proximal and distal guidewires were then removed and a quadripolar non-fixative electrode[3] was introduced through both the proximal and distal introducer catheter and advanced into the right atrium (see figure 10). One quadripolar electrode functioned as the atrial pacing electrode while the other electrode was for registration. The electrodes were placed in the right atrium in a position resulting in the appearance of a signal on the intracardiac electrocardiogram in close association with the beginning of the P wave on the surface electrocardiogram and where consistent atrial capture was achieved when pacing at 1000 milliseconds. In addition, to ensure that the pacing P wave was not misinterpreted as a pacing artifact the morphology of the paced P wave should be similar to the P wave morphology obtained during sinus rhythm. If deflections on the intracardiac electrocardiogram appeared coinciding with the beginning of the QRS complex on the surface electrocardiogram the pacing electrode was repositioned backwards into the atrium.

[1] Xylocaine, 20 mg/ml, AstraZeneca A/S, Copenhagen, Denmark

[2] 8F percutaneous introducer, Argon Medical Devices, USA

[3] St. Jude Medical, Inc, Minnesota, USA

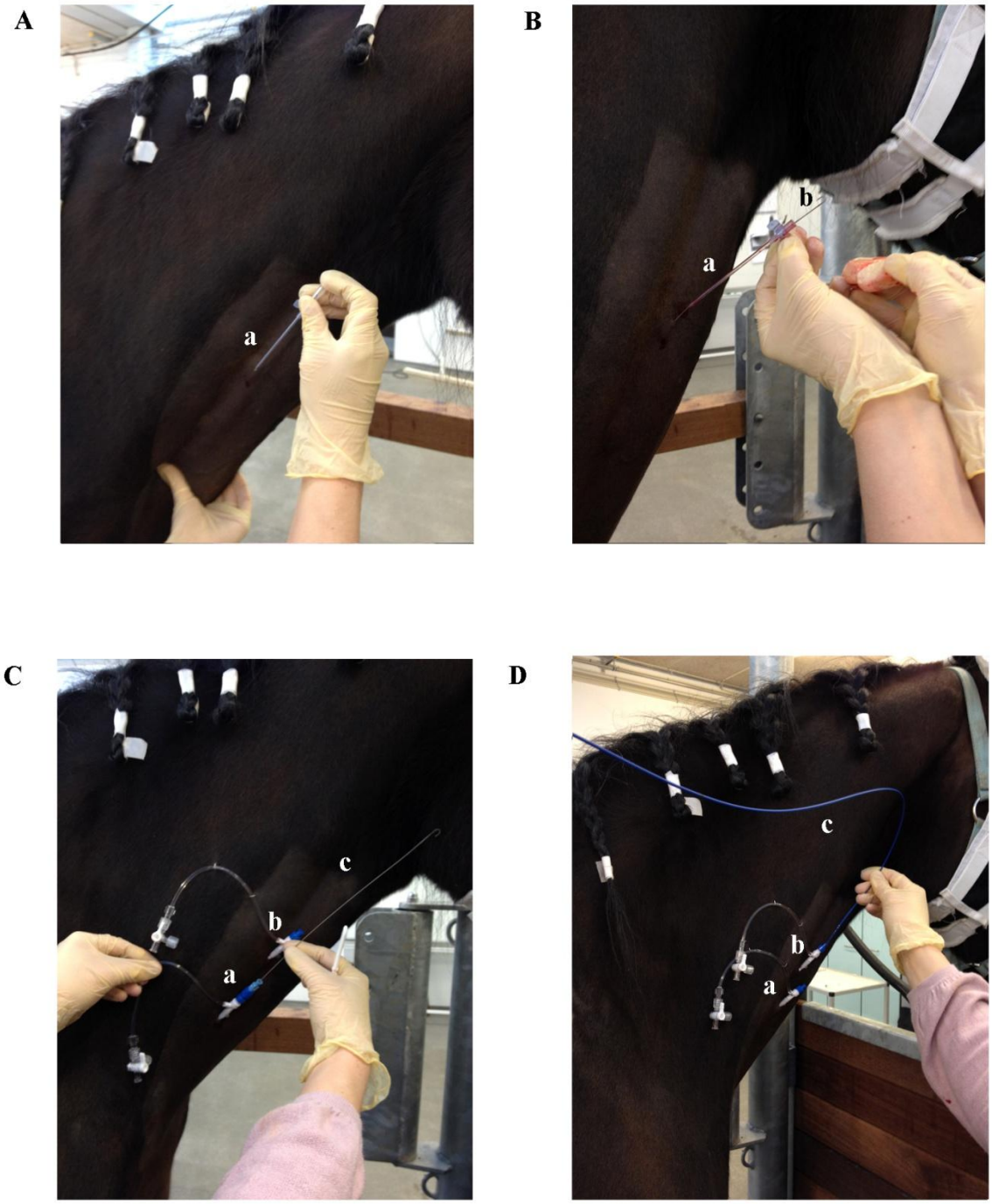

Figure 10 Frame A. A 12G catheter (a) is being placed in the right jugular vein. **Frame B.** A guidewire (b) has been placed in the 12G catheter. The 12G catheter is being removed so that only the guidewire is placed in the vein. **Frame C.** Proximal and distal introducer catheters (a and b) have been placed in the right jugular vein. A guidewire (c) from the proximal introducer catheter is being removed. **Frame D.** Proximal and distal introducer catheters (a and b) have been placed in right jugular vein. A quadripolar non-fixative electrode (c) is being introduced through the distal introducer catheter.

4.2.1.2 Surface electrocardiogram

Two surface electrocardiograms (ECGs) were recorded simultaneously with the intracardiac electrocardiogram using a modified base-apex lead and a P wave lead (figure 11). Self-adhesive ECG electrodes[4] were attached to the skin. To improve skin contact the horse was clipped before the electrodes were attached. The modified base-apex ECG was placed with the negative electrode located on the upper part of the right scapula, corresponding to the base of the heart. The positive electrode was positioned over the apex of the heart, on the left side of the sternum at the sixth inter-costal space. The reference electrode was positioned on the left scapula. The P wave lead was placed with the negative electrode on the upper right scapula, the reference electrode on the upper left scapula, and the positive electrode in front of the girth at the base of the heart. This electrode position was adjusted to obtain a P wave with large amplitude on the surface ECG. The electrodes were connected to the software program, Labchart[5]. For a back up during the studies, an ambulatory ECG was recorded using a modified base-apex lead system. The negative (red) electrode was positioned over the base of the heart on the right scapula. The positive (green) electrode was positioned over the apex of the heart, on the left side of the sternum. The yellow electrode was placed on the left side of the horse behind the saddle. The remaining reference (black) electrode was positioned next to the red electrode. The electrodes were connected to the recording device, Televet 100[6], with 4 electrode cables.

[4] Kruuse A/S, Langeskov, Denmark

[5] Animal Bioamplifier, ADInstruments Ltd, Oxford, UK

[6] Kruuse A/S, Langeskov, Denmark

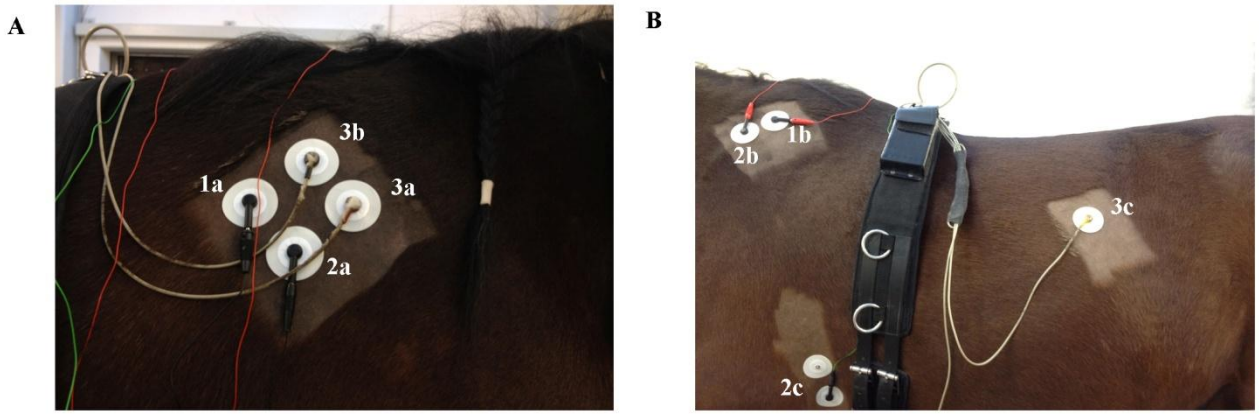

Figure 11 Modified base-apex lead system (1a-b), P wave lead system (2a-c), and ambulatory modified base-apex lead system (3a-c) seen from right side (A) and left side (B) of a horse. **A. Right side**. 1a: Negative electrode of the modified base-apex lead system. 2a: Negative electrode of the P wave lead system. 3a: Negative electrode (red) of the ambulatory modified base-apex lead system. 3b: Reference electrode (black) of the ambulatory modified base-apex lead system. **B. Left side**. 1b: Reference electrode of the modified base-apex lead system. Positive electrode of the modified base-apex lead system is not seen. 2b: Reference electrode of the P wave lead system. 2c: Positive electrode of the P wave lead system. 3c: Positive electrode (yellow) of the ambulatory modified base-apex lead system. The positive green electrode of the ambulatory modified base-apex lead system is not seen.

4.2.1.3 Electrophysiologic measurements

Before initiation of electrophysiological measurements a threshold (rheobase) was found. The threshold was defined as the lowest amplitude that consistently captured the atrium. To be certain that atrial capture was consistent throughout measurements the amplitude was set to two times threshold. For atrial threshold determination a stimulus reduction method as described by van Loon *et al*. was used (van Loon et al., 2001). The pulse width (PW) is programmed at a fixed value. Pacing stimulation starts with high amplitude and is gradually decreased until capture is lost. In this study the threshold for stimulation was determined at a basic cycle length (BCL) of 1000 milliseconds and a PW of 2 milliseconds. The amplitude was set to 10 mA and decreased stepwise 1 mA until capture was lost. Capture was present as long as every electrical stimulus was followed by a P wave on the surface ECG. When the amplitude became too low, a P wave was not initiated, capture was lost, and intrinsic heart rate reappeared.

The atrial effective refractory period (aERP) before drug administration was measured at 2 times threshold amplitude and at a pulse width of 2 milliseconds. The aERP was determined by pacing the atrium with 8 stimuli (S1) at a BCL of 1000 (60 beats/min), 800 (75 beats/min.), 500 (120 beats/min.), and 330 (182 beats/min) milliseconds, respectively. An extra stimulus (S2) was

introduced after 8 S1 stimuli with a coupling interval (S1-S2) below the expected refractory period. The S1-S2 interval was increased in steps of 10 milliseconds intervals until capture of the extra stimulus was achieved; the atrial S2 was followed by a P wave on the surface ECG. The atrial effective refractory period was the longest S1-S2 interval that did not result in capture of the atrium for the respective cycle length (S1-S1) (figure 12). The above described procedure was repeated after drug administration.

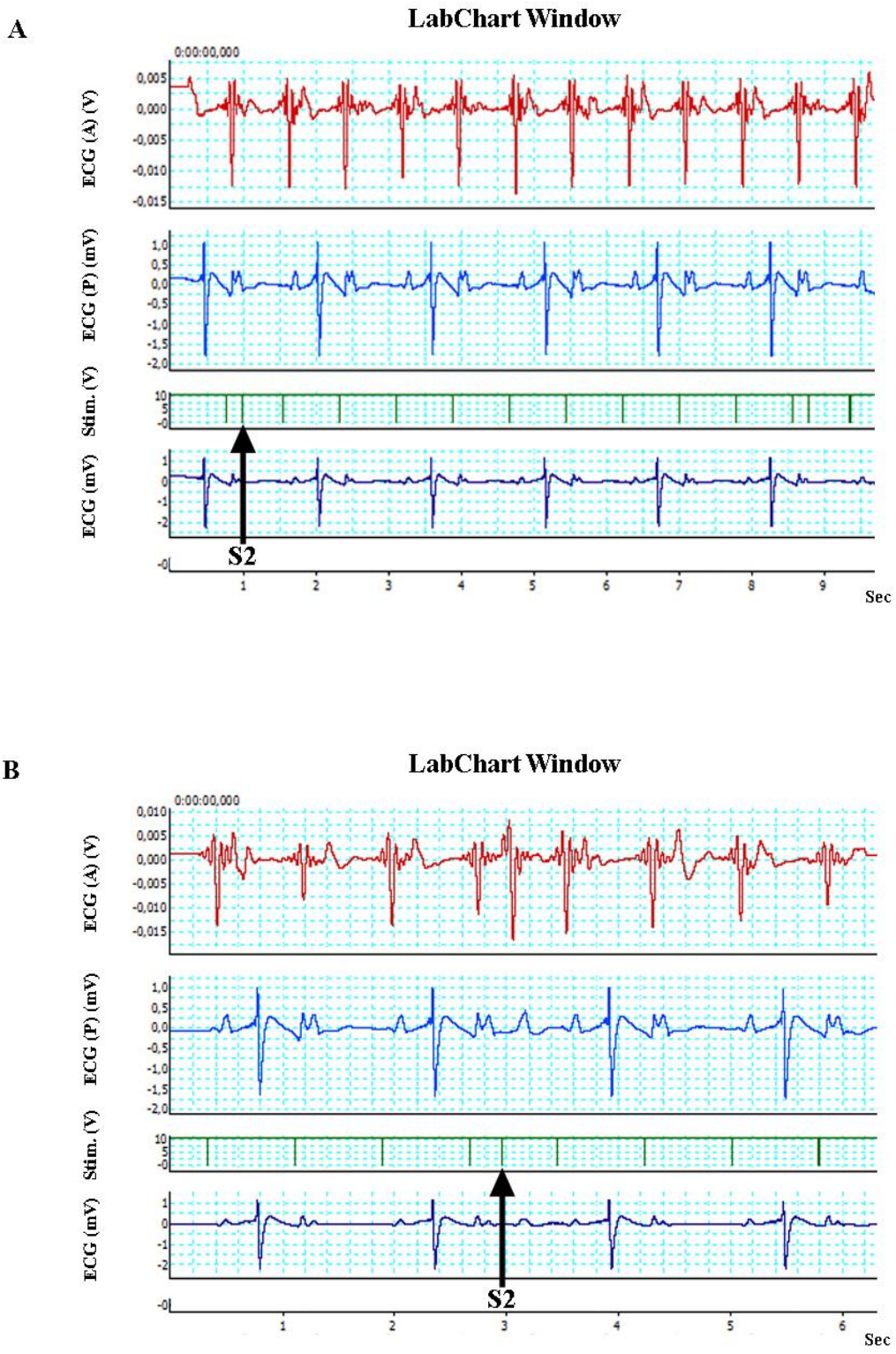

Figure 12 Atrial pacing. **A**. An extra stimulus (S2) does not result in atrial capture. **B**. An extra stimulus (S2) resulting in atrial capture. The atrial S2 was followed by a P wave on the surface ECG (ECG and ECG (P)) and a signal on the intracardiac electrogram (ECG (A)). ECG recordings obtained during the study procedures.

Tachypacing was applied to induce atrial fibrillation (AF) as previously described by van Loon *et al.* and by De Clercq *et al.* (van Loon et al., 2000, De Clercq et al., 2008b). The amplitude was 2 times threshold and the PW 2 milliseconds. AF induction at BCL 200 milliseconds (=5 Hz) for 2-3 seconds was applied, and the outcome was evaluated. This was tried at a minimum of 5 times. If AF was not induced the BCL was then reduced to 100 (=10 Hz) or 20 (=50 HZ) milliseconds. If AF still was not induced the amplitude was increased to 10 mA. The duration of the induced AF episodes was measured by switching the pulse generator off after a burst was delivered and recording the time needed for sinus rhythm to restore. After restoration of sinus rhythm, the pulse generator was switched on and off again to measure new AF episodes. This was done 15 times with ½-1 minutes recovering in sinus rhythm between inductions to obtain a mean value and range for AF duration. If AF episodes were long (more than 5 minutes) AF induction was only repeated 5 times. Sustained AF was defined as AF of more than 15 minutes duration and the antiarrhythmic drug was then given. After drug administration AF was induced again to measure the effect of the antiarrhythmica. The BCL (200//100/20 milliseconds) that was able to induce AF before drug administration was used to induce AF after drug administration. Induction was tried at a minimum of 5 times. If AF did not occur or the AF episodes were shorter than before drug administration, the drug was considered effective, having an antiarrhythmic effect in the atrium. The duration of the induced AF episodes was measured if AF occurred. After restoration of sinus rhythm, the pulse generator was switched on and off again to measure new AF episodes. As before drug administration, this was done 15 times with ½-1 minutes recovering in sinus rhythm between inductions in order to obtain a mean value and range for AF duration. If AF episodes were long (more than 5 minutes) AF induction was only repeated 5 times. See figure 13 for study procedure.

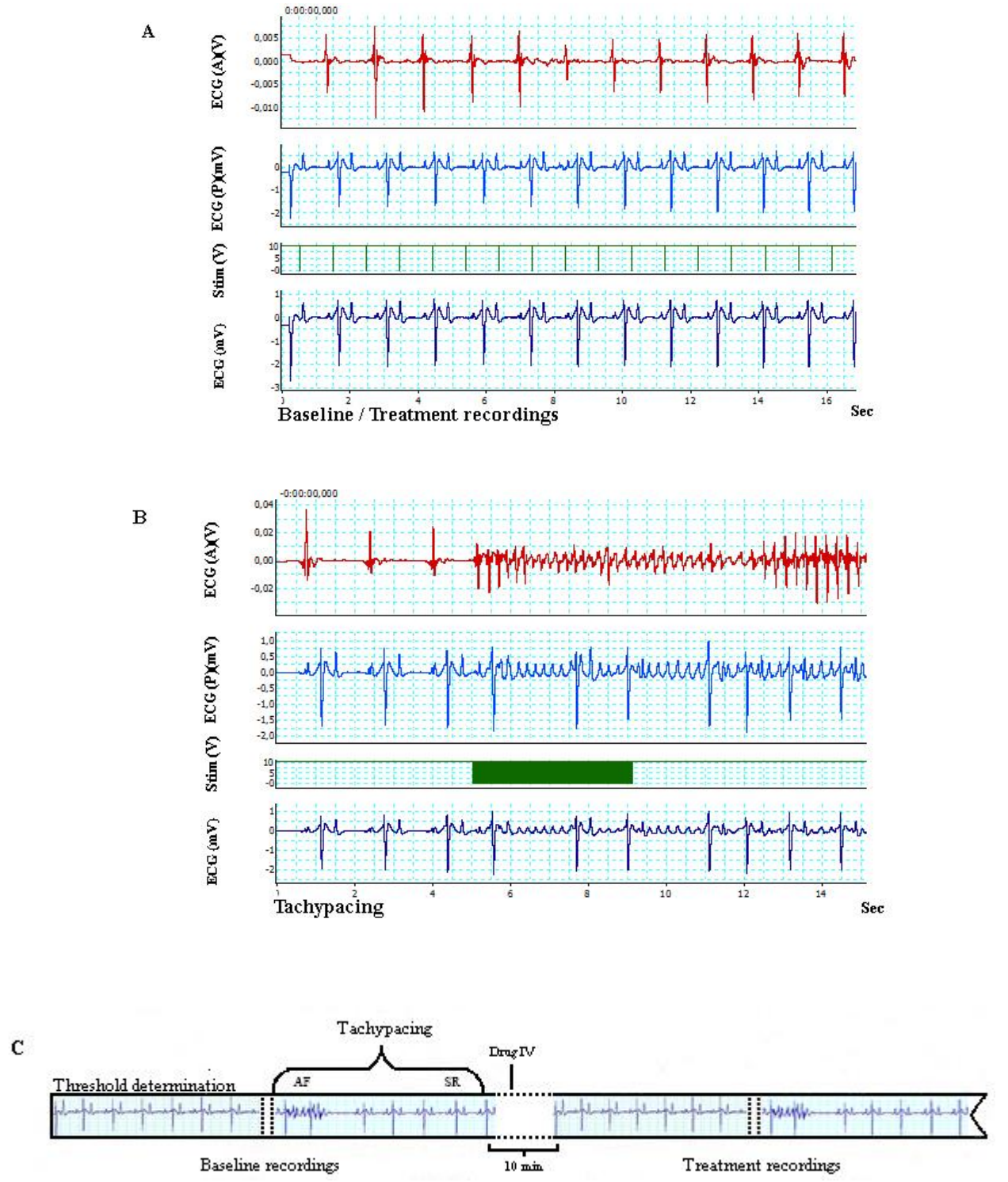

Figure 13 Representative pictures of the study procedures. **A.** Baselinie/treatment recordings. ECG: Surface electrocardiogram; modified base-apex lead system, Stim.: Intraatrial stimulation, ECG(P): surface electrocardiogram; P wave lead system, ECG(A): intracardiac electrocardiogram. **B.** Tachypacing resulting in atrial fibrillation. **C.** Schematized timeline of the study procedure. For a detailed description of the study procedure, please refer to the methods.

After the procedure, the horses were given penicillin[7] (5ml/100 kg) twice a day for 3 days, monitored for any abnormal clinical symptoms and the surface ECG (Televet) was left in place for 12-24 hours after the procedure.

4.2.2 Electrocardiography during the unconscious procedure

4.2.2.1 Catheterization and general anesthesia

Catheterization was achieved by a standard protocol, as described previously during the conscious procedure. All catheters were placed in the conscious horse to facilitate correct catheter position. After catheter placement, general anesthesia was induced. The horse was premedicated with a combination of detomidine[8] (1mg/100kg) and acepromazine[9] (3mg/100kg) intravenously before induction. Induction was achieved with butorphanol[10] (3mg/100kg) intravenously and after 5 minutes zoletil[11] (140-180mg/100kg) intravenously. Maintenance of anesthesia was then initiated with isoflurane inhalation[12]. Intravenous lactated Ringer's solution was administered throughout the procedure. Dobutamine[13] (1-10 micrograms/kg/minute IV) was administered if required to maintain mean arterial blood pressure above 60 mmHg. The quadripolar non-fixative electrode and a screw-in electrode[14] were placed after general anesthesia to avoid catheter movement and damage. The screw-in electrode was the electrode used for pacing. This electrode was placed in the right atrium by fluoroscopic guidance[15] and modified if consistent atrial capture was not achieved when pacing at 1000 milliseconds. After placement of the screw-in electrode, the quadripolar non-fixative electrode was positioned by fluoroscopy at a place where a signal on the intracardiac electrogram appeared in close association with the beginning of the P wave on the surface electrocardiogram. In

[7] Penovet Vet, 300.000 U/ml, Boehringer Ingelheim Danmark A/S, Copenhagen, Denmark

[8] Domosedan Vet, 10 mg/ml, Orion Pharma A/S, Nivå, Denmark

[9] Calmivet, 5 mg/ml, Vétoquinol, ScanVet Animal Health A/S, Fredensborg, Denmark

[10] Torbugesic Vet, 10 mg/ml, ScanVet Animal Health A/S, Fredensborg, Denmark

[11] Zoletil 50 Vet, 50 mg/ml, Virbac Danmark A/S, Kolding, Denmark

[12] VetFlurane, 250 ml, Virbac Danmark A/S, Kolding, Denmark

[13] Dobutrex, 12,5 mg/ml, Nordmedica A/S, Gentofte, Denmark

[14] CapSureFix Novus 5076, Medtronic Inc., Minnesota, USA

[15] Siremobil Compact L, Siemens AG, Erlangen, Germany

addition, to ensure that the pacing P wave was not misinterpreted as a pacing artifact, the morphology of the paced P wave should be similar to the P wave morphology obtained during sinus rhythm. To be able to use fluoroscopy to place the electrodes in the right atrium, the horse was place in dorsal recumbency and the front legs placed as far cranial as possible.

4.2.2.2 Surface electrocardiogram

Two surface electrocardiograms were attached after general anesthesia was achieved. The same lead systems as during the conscious procedures were recorded during the unconscious procedures. Also, as during the conscious procedures a back up ambulatory electrocardiogram was recorded using a modified base-apex lead system.

4.2.2.3Electrophysiologic measurements

The electrophysiologic measurements were carried out as described in the standing procedure. The SK-negative modulator NS8593 (5 mg/kg) was given intravenously over 10 minutes to four of the six horses included in the study. Because NS8593 is currently under development, the pharmacokinetic properties of this drug candidate are not completely examined. Hence, there is a potential risk that the drug may cross the blood-brain-barrier and thereby cause convulsions (Strøbæk et al., 2006). The horses were therefore anesthetized during this procedure. If convulsions occurred, diazepam (25-50 mg)[16] was administered intravenously. Two horses were given flecainide during anesthesia to investigate the effect of anesthesia on the aERP, AF duration and QTc intervals. However, these results are not included in this thesis as several horses are required to investigate this further.

After the procedure all horses were euthanized with pentobarbital (44 mg/kg) during anesthesia.

4.3 ECG analysis

The ECG recordings were analyzed using the provided software program (Labchart 7) and time intervals were analyzed manually using on screen electrocardiographic tools.

[16] Stesolid Emulsion, 5 mg/ml, Actavis A/S, Gentofte, Denmark

Recording periods (t= -5 to 13) were identified in the modified base-apex P wave lead system and QT intervals were measured on 5 consecutive beats within each recording period. QT intervals were measured just before drug administration (t=-1), and at 5 (t=-2), 10 (t=-3), 15 (t=-4), and 20 (t=-5) minutes before drug administration, immediately after starting drug administration (t=1), 1 (t=2), 2 (t=3), 3 (t=4), 4 (t=5), 5 (t=6), 10 (t=7), 15 (t=8), 20 (t=9), 25 (t=10), 30 (t=11), 45 (t=12), and 60 (t=13) minutes after drug administration.

4.4 Data analysis and statistics

To minimize the possible effect of QT lag QT intervals were adjusted with a weighted average of the preceding five RR intervals. The modified RR interval RRmod was defined as follows: RRmod = (5*RRn-1 + 2*RRn-2 + RRn-3 +RRn-4 +RRn-5)/10, where RRn-1 is the RR interval just previous to a QT interval, RRn-2 the second interval, and so forth. This method demonstrates that the beat immediately preceding the QT interval has the highest weight in QT adaption and then slowly declines the further the RR interval is from the measured QT interval (figure 14).

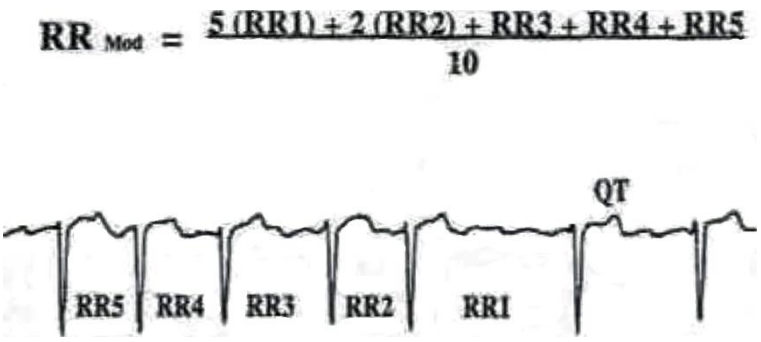

Figure 14 The weighted average RR interval. Modified from Ehlert *et al.* (1992).

Due to heart rate effects on the QT interval the QT intervals were corrected for heart rate. In this study the QT intervals were corrected using Bazett's formula for correction (QTc=QT/√RR).

All data was analyzed by use of Excel[17] and further processed with Graph Pad Prism[18]. For assessment of the effects of flecainide and NS8593 on QT intervals one-way repeated-measures analysis of variance (ANOVA) was used to compare QT intervals across treatment periods. Where

[17] Microsoft Office Excel 2007, Microsoft Corporation, Redmond, USA

[18] GraphPad Software Inc., CA, USA

the test statistics indicated significant differences, all pairwise comparisons were performed using Dunnett's multiple comparison test. The time -1, which was just before drug infusion, was used as the reference time.

5. Results

5.1 Conscious study

Intravenous administration of flecainide at a dose of 2 mg/kg IV over 10 minutes was well tolerated by all horses included in the study. No clinical signs of adverse side effects were observed.
A protocol including aERP measuring at different heart rates and induction of atrial fibrillation with S2 stimulation or tachypacing was conducted before drug application (n=6). Four horses converted to sinus rhythm with an average time of 4.77 ±1.76 minutes after initiation of intravenous drug administration (n=4). However, induction of atrial fibrillation was not achieved in two horses following the induction protocol and flecainide was given in sinus rhythm (n=2) (Table 1).

A one-way repeated-measures analysis of variance (ANOVA) of the QTc interval measurements confirmed a statistical significant difference between QTc mean values. When QTc mean values were pitted against the reference mean value in Dunnett's multiple comparison test QTc mean values at 15, 20 and 25 minutes (time: 8, 9 and 10, respectively) following flecainide administration were declared significantly prolonged ($P<0.05$) from the reference mean value. The reference value consisted of the QTc means at time -1, which was just before drug treatment. The reference QTc mean averaged 471.34 ±39.83 msec. QTc maximum occurred 15 minutes after flecainide administration, reaching an average of 568.01 ± 26.64 msec (figure 15). See Appendix A, table 2 for measurements and calculations, and Appendix B, table 4-5 for analysis.

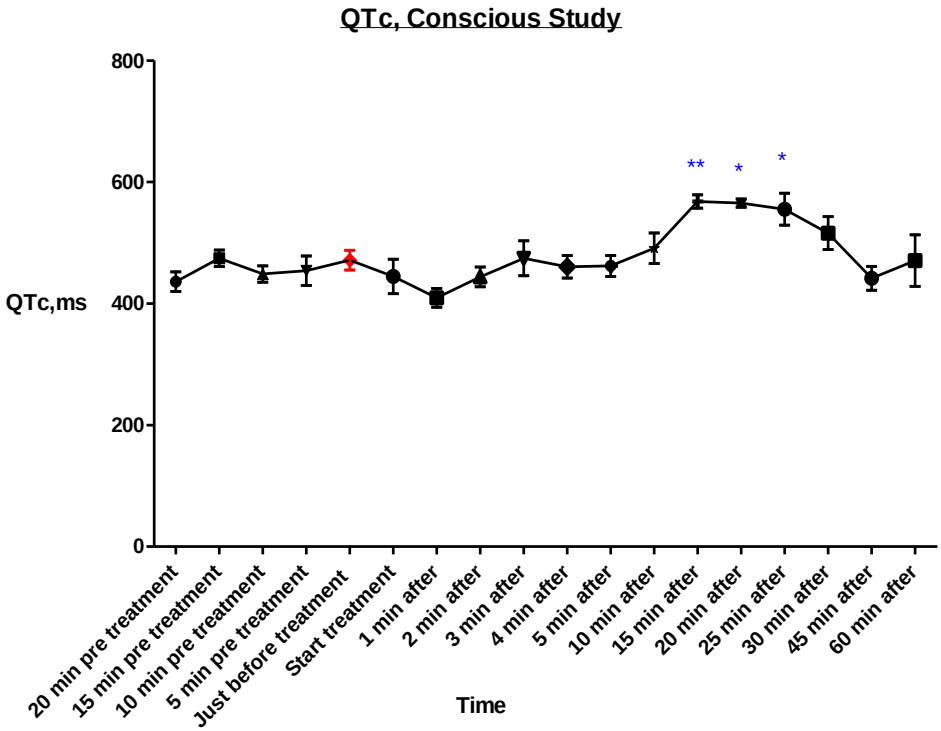

Figure 15 Colum mean graph of QTc mean values± SD in the conscious study. QTc mean values at 15, 20 and 25 minutes (time: 8, 9 and 10, respectively) following infusion were significantly prolonged ($P<0.05$) (level of significance: */**) from the mean of the reference value. The reference value (red) consisted of the QTc means just before drug treatment (time: -1).

The present conscious study has focused on the QTc interval to investigate the efficacy and safety of flecainide in equine cardiology. However, to further assess the outcome of the study QRS complexes, JTc intervals and HR measurements were included as these data further supported the results of the present study.

A one-way repeated-measures ANOVA of the QRS interval measurements confirmed a statistical significant difference between QRS mean values. In a Dunnett's multiple comparison test QRS mean values at 10, 15, 20 and 25 minutes (time: 7, 8, 9 and 10, respectively) following infusion of flecainide were significantly prolonged ($P<0.05$) from the reference mean value. The reference value consisted of the QRS means at time -1, which was just before drug treatment. The QRS reference mean value averaged 146.8 ±12.28 msec. QRS maximum occurred 15 minutes after flecainide administration, reaching an average of 164.08 ±19.87 msec (figure 16). See Appendix A, table 2 for measurements and calculations, and Appendix B, table 6-7 for analysis.

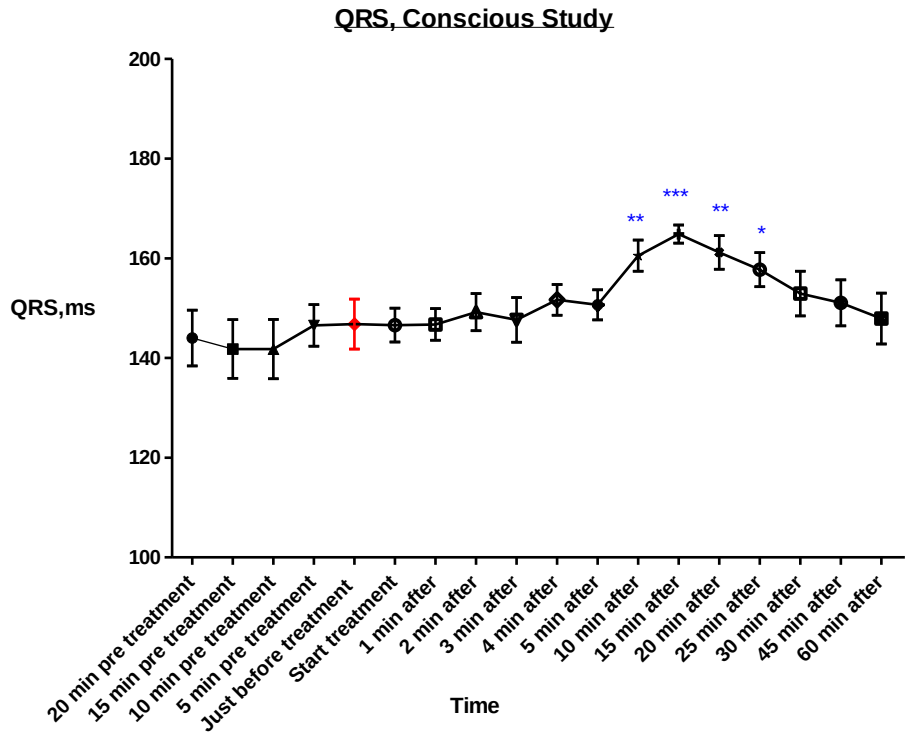

Figure 16 Colum mean graph of QRS mean values± SD in the conscious study. QRS mean values at 10, 15, 20 and 25 minutes (time: 7, 8, 9 and 10, respectively) following infusion were significantly prolonged ($P<0.05$) (level of significance: */**/***) from the reference mean value. The reference mean value (red) consisted of the QRS means just before drug treatment (time: -1).

The JTc intervals were calculated as QTc-QRS. A one-way repeated-measures ANOVA of the JTc interval measurements confirmed a statistical significant difference between JTc mean values. However, in a Dunnett's multiple comparison test no JTc mean values were significant different ($P>0.05$) from the reference mean value. The reference mean value consisted of the JTc means at time -1, which was just before drug treatment. Although Dunnett's test did not contribute additional information, an increase 15, 20 and 25 minutes after flecainide infusion was observed (see figure 17). See Appendix A, table 2 for measurements and calculations, and Appendix B, table 8-9 for analysis.

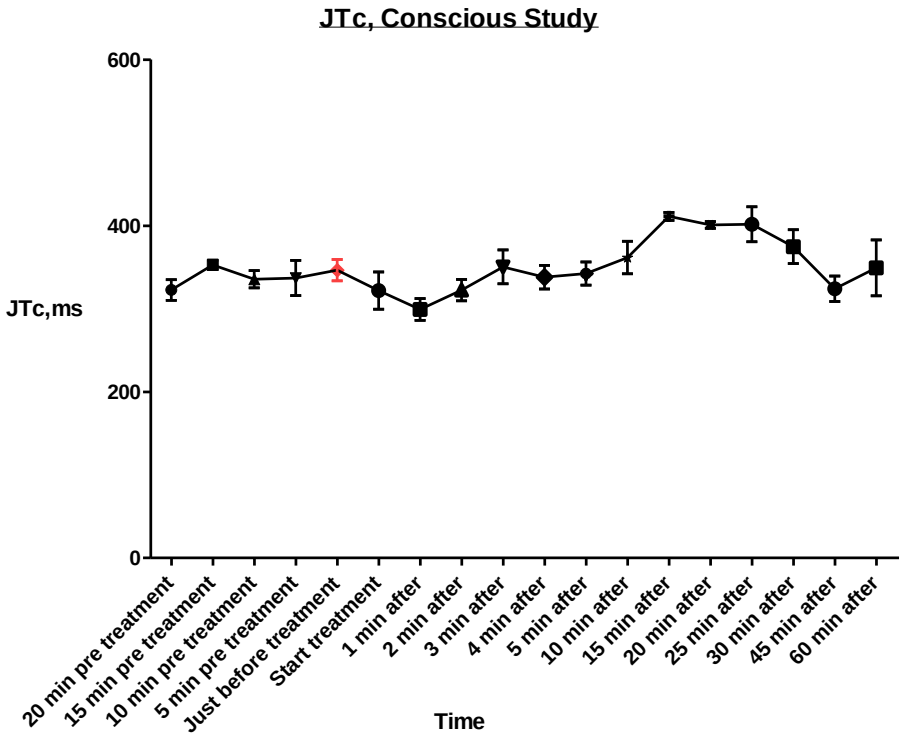

Figure 17 Colum mean graph of JTc mean values± SD in the conscious study. In a one-way repeated-measures ANOVA JTc mean values were significantly different. Although not significantly prolonged (P>0.05) in a Dunnetts multiple comparison test, an increase in JTc mean values 15, 20 and 25 minutes after flecainide infusion was observed. The reference mean value (red) consisted of the JTc mean values just before drug treatment (time: -1).

A one-way repeated-measures ANOVA of HR over time confirmed a statistical significant difference between HR mean values. When HR mean values were pitted against the reference mean value in Dunnett's multiple comparison test HR mean values at 20 minutes (time: 9) following flecainide administration were significantly prolonged (P<0.05) from the reference mean value. The maximum increase averaged 62.96 ±12.92 bpm. The reference mean value averaged 42.91 ±8.33 bpm. In addition, the HR increased, although not significantly, at 15 and 25 minutes after flecainide infusion. The reference mean value consisted of the HR means at time -1, which was just before drug treatment (figure 18). See Appendix A, table 2 for measurements and calculations, and Appendix B, table 10-11 for analysis.

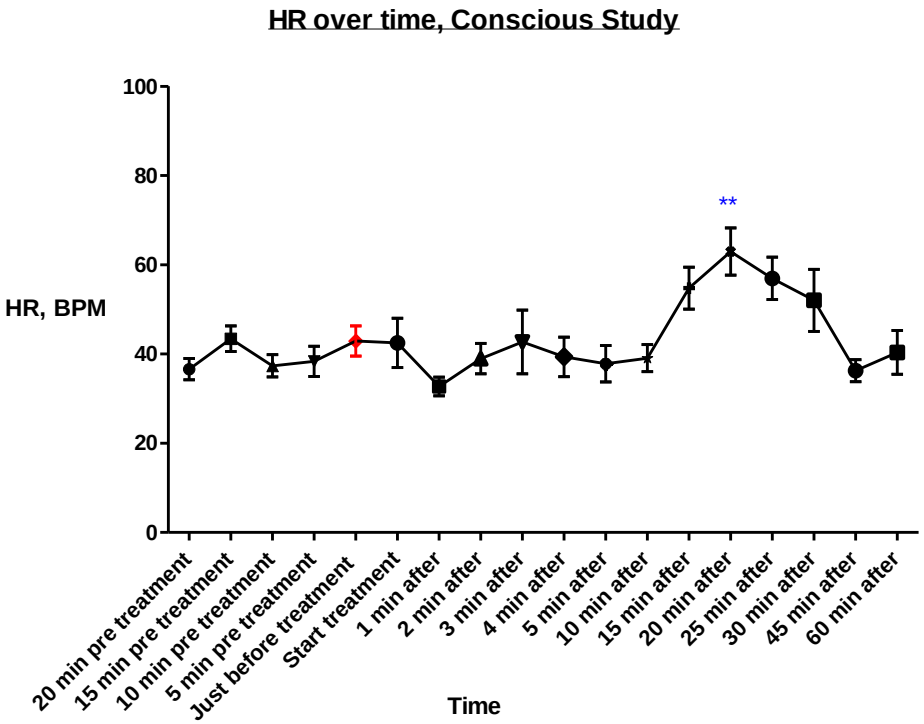

Figure 18 Colum mean graph of HR mean values± SD in the conscious study. HR mean values at 20 minutes following infusion were significantly prolonged (P<0.05) (level of significance: **) from the reference mean value. The reference mean value (red) consisted of the HR means just before drug treatment (time: -1).

5.2 Unconscious study

The capability of NS8593 at a dose of 5 mg/kg administered intravenously over 10 minutes and flecainide at a dose of 2 mg/kg intravenously over 10 minutes to revert atrial fibrillation was investigated in six anesthetized horses. Four horses were given NS8593, while two horses were given flecainide. Intravenous administration of flecainide was well tolerated in both horses receiving flecainide, while convulsions were observed during or shortly after administration of NS8593 in three of four horses.

A protocol including aERP measuring at different heart rates and induction of atrial fibrillation induced by S2 stimulation or tachypacing was conducted before drug application (n=6). However, induction of atrial fibrillation was not achieved in one horse following the induction protocol and NS8593 was given in sinus rhythm (n=1). One of two horses receiving flecainide converted to sinus rhythm 14.08 minutes after starting drug administration, while the other horse receiving flecainide

did not convert despite treatment and was euthanized in atrial fibrillation. All horses receiving NS8593 in atrial fibrillation (n=3) converted to sinus rhythm with an average time of 10.22 ± 1.87 after initiation of drug administration (Table 1).

Horse ID	Conscious study		Unconscious study	
	Time to convert (min.)	Antiarrhythmic drug	Time to convert (min.)	Antiarrhythmic drug
8	6.01	Flecainide	14.08	Flecainide
9	DiSR	Flecainide	NC	Flecainide
10	DiSR	Flecainide	11.01	NS8593
11	2.35	Flecainide	11.57	NS8593
12	6.14	Flecainide	8.08	NS8593
13	4.58	Flecainide	DiSR	NS8593
	Mean ± SD 4.77 ±1.76		For NS8593: Mean ± SD 10.22 ± 1.87	

Table 1 Summary of flecainide and NS8593 treatment to conversion of pacing-induced atrial fibrillation in conscious and unconscious horses. DiSR: drug in sinus rhythm, NC: no conversion.

A comparison of QTc mean values for the horses receiving NS8593 was conducted. No significant differences between the QTc mean values were found using one-way repeated-measures ANOVA and no QTc mean value was significantly prolonged ($P>0.05$), when compared to the reference mean value in a Dunnett's multiple comparison test (figure 19). See Appendix A, table 3 for measurements and calculations, and Appendix B, table 12-13 for analysis.

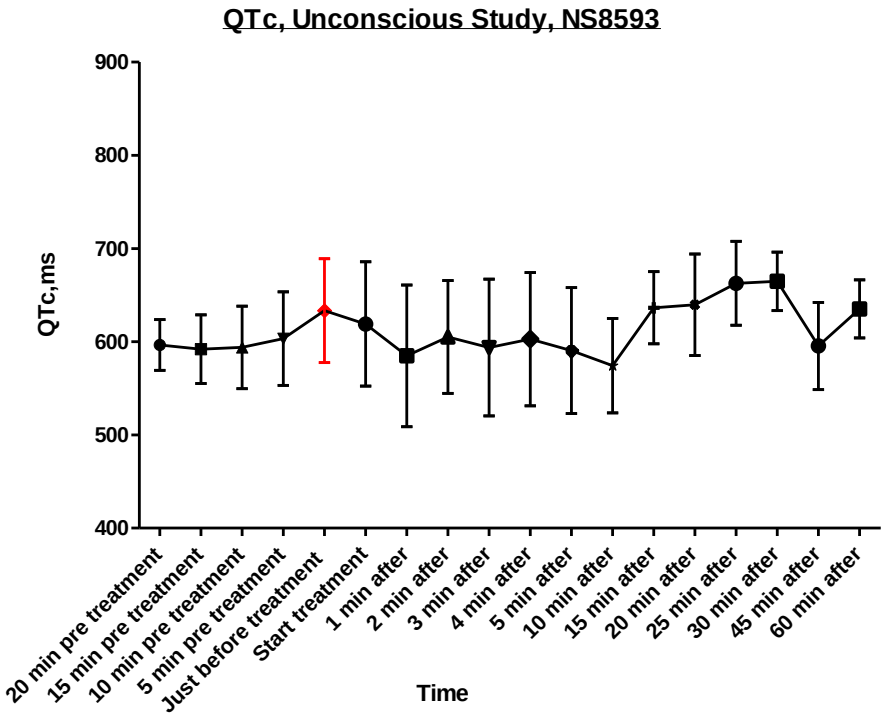

Figure 19 Colum mean graph of QTc mean values± SD in the unconscious study. No significant differences (P>0.05) between the QTc mean values were found. The reference mean value (red) consisted of the QTc means just before drug treatment (time: -1).

Only two horses were given flecainide in the unconscious study and one of these horses was euthanized shortly after drug infusion. Thus, QTc data from the two horses were excluded from the study.

As in the conscious study heart rates were measured and analyzed using one-way repeated-measures ANOVA. No significant differences between the HR mean values were found between HR mean values. A non-significant increase (P>0.05) between HR mean values was found at 20, 25 and 30 minutes after drug infusion in a Dunnett's multiple comparison test (figure 20). See Appendix A, table 3 for measurements and calculations, and Appendix B, table 14-15 for analysis.

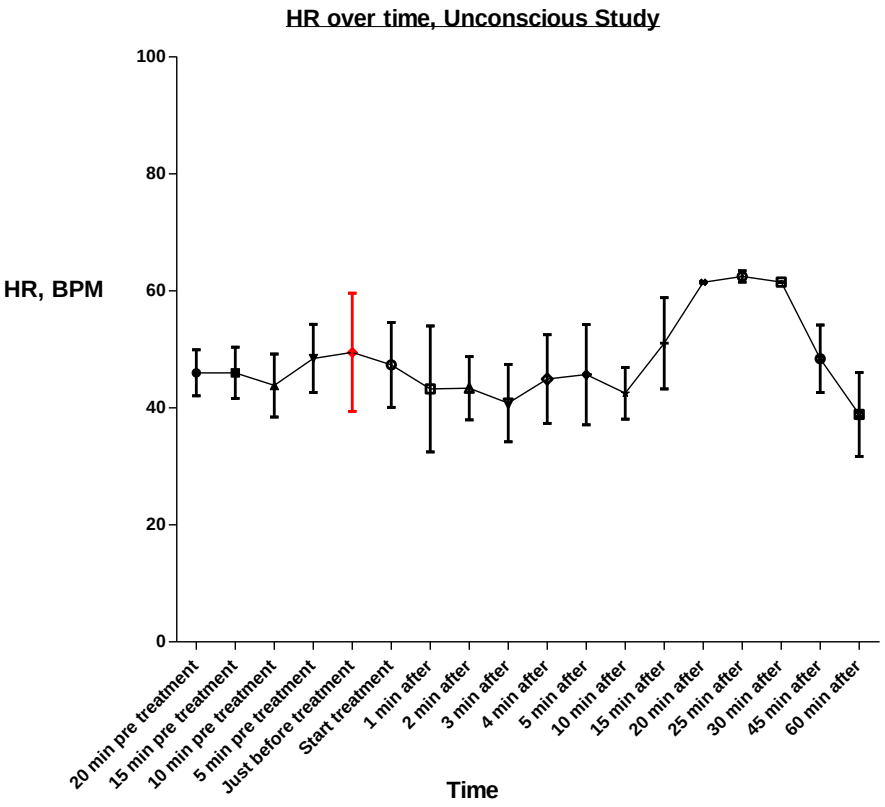

Figure 20 Colum mean graph of HR mean values± SD in the unconscious study. A non-significant (P>0.05) increase in HR mean values was found at 20, 25 and 30 minutes following infusion. The reference mean value (red) consisted of the HR means just before drug treatment (time: -1).

6. Discussion

In the present study a pacing-induced acute model for atrial fibrillation was used to examine the safety and efficacy of flecainide and NS8593. As outlined in the introduction the goal of this thesis was to evaluate the antiarrhythmic potential of NS8593 and flecainide in equine cardiology by focusing on the QT-interval.

In the present conscious study sinus rhythm could be restored in all horses in atrial fibrillation receiving 2 mg/kg of flecainide intravenously. In addition, no clinical adverse side effects, such as colic and diarrhea, were seen in relation to drug administration. These observations were in accordance with the findings of Ohmura *et al*., who reported successful intravenous treatment of six horses with 2 mg/kg of flecainide (Ohmura et al., 2000). The results can probably be explained by the fact that healthy horses with transient experimentally-induced atrial fibrillation were studied. Usually, atrial fibrillation is more organized immediately after experimental induction but when maintained for prolonged periods electrical remodeling can occur, resulting in increased stability of atrial fibrillation (Wijffels et al., 1995). Horses with short-term atrial fibrillation are therefore more easily converted to sinus rhythm compared to horses with longstanding atrial fibrillation (Reef et al., 1988). Improved efficacy of flecainide in treating acute compared to chronic atrial fibrillation is also reported in the human literature (Suttorp et al., 1989, Kingma and Suttorp, 1992). Short-term rapid atrial pacing in horses with normal atrial function and size is likely to be different from natural atrial fibrillation in patients with remodeled or diseased atrial tissue. This was also demonstrated by van Loon *et al*., who studied the efficacy of intravenous flecainide as a treatment for atrial fibrillation in horses with naturally-occurring atrial fibrillation (van Loon et al., 2004). Van Loon *et al.* reported that although flecainide might be an efficacious antiarrhythmic drug for medical cardioversion of acute atrial fibrillation, it has limited potential in treating naturally-occuring chronic cases and might even induce potentially dangerous arrhythmias (van Loon et al., 2004).

The results of the conscious study indicate that 2 mg/kg of flecainide administered intravenously can prolong the QTc interval in horses. The significant QTc prolongation was observed at 15, 20, and 25 minutes after initiation of flecainide infusion in the conscious study. However, all horses in atrial fibrillation converted to sinus rhythm within a few minutes after initiation of flecainide

infusion. Therefore, it was speculated that flecainide converted horses in atrial fibrillation to sinus rhythm, while an active metabolite was responsible for the observed late QTc prolonging effect. The presence of active metabolites of antiarrhythmic drugs can explain an unanticipated therapeutic effect or toxicity (Woosley and Roden, 1983). Biotransformation of flecainide in man results in the production of two major metabolites, S-24623 and S-26191, and the cardiac electrophysiologic effects of these two metabolites have been investigated in the canine heart (Guehler et al., 1985). Guehler *et al.* reported that despite qualitative similarities between electrophysiologic effects of flecainide and its principal metabolites, both S-24623 and S-26191 lack the potency of the parent compound (Guehler et al., 1985). Consequently, given the relatively low concentration of unconjugated metabolites in plasma it is unlikely that the metabolites would either potentiate flecainide's antiarrhythmic effect or increase susceptibility to flecainide-induced toxicity (Conard and Ober, 1984, Guehler et al., 1985). However, the metabolism of flecainide in horses has not been investigated thoroughly. Thus, investigation of the metabolism of flecainide in horses is acquired to assess this theory further.

Flecainide is a class 1c antiarrhythmic agent known to act primarily on the fast sodium channels, depress the rate of depolarization and slow intracardiac conduction. In addition, flecainide prolongs the refractory period. The effect on refractoriness is however less pronounced (Holmes and Heel, 1985). The decreased conduction velocity results in a QRS prolongation. It was therefore suggested that the observed QTc prolongation was mainly the result of a QRS widening. A significant QRS widening at 10, 15, 20 and 25 minutes after drug infusion was observed when measuring and analyzing QRS complexes. Based on these data, the QT prolongation resulted mainly from QRS widening and not from prolongation of ventricular repolarization. This is consistent with similar results obtained from human cardiac electrophysiologic studies and in accordance with the electrophysiological properties of flecainide (Hellestrand et al., 1982, Estes Iii et al., 1984).
As previously described in this thesis flecainide prolongs the repolarization phase by ERG channel blockade. To evaluate the ERG blockade effect on the QTc interval in the present study the JTc interval (QTc - QRS) was measured. The JTc is an index of ventricular repolarization in order to exclude errors resulting from drug-induced prolongation of the QRS complex (i.e. depolarization), and has been reported to be a more appropriate measure of ventricular repolarization than QTc alone (Spodick, 1992, Crow et al., 2003). An increase in the JTc interval was observed 15, 20 and 25 minutes after flecainide infusion indicating that this drug affects the ventricular repolarization.

However, JTc interval prolongation was observed at higher heart rates. Thus, it was suggested that the observed JTc prolongation was primarily caused by the heart rate correction method used in this study and not an actual JTc prolongation. Although not significant at all times, an increase in heart rate was observed 15, 20 and 25 minutes after intravenous administration of flecainide. It is a well-known fact that the QT interval is inversely related to heart rate; the slower the heart rate the longer the QT interval. The QT intervals in the study were therefore "corrected" for heart rate using Bazett's equation to minimize the correlation between the QT interval and RR intervals. However, Bazett's correction method over-corrects QTc at higher heart rates resulting in a prolongation of the QTc intervals (Indik et al., 2006).

Analysis of variance showed that flecainide increased heart rate 15, 20 and 25 minutes after infusion. During this period the horses were not being handled further and there was no clinical evidence of stress or discomfort. Experimental studies in animals have shown a dose-related negative inotropic effect of flecainide (Verdouw et al., 1979, Schulze and Knops, 1982). A previous study in humans have demonstrated that intravenous flecainide at a dosage of 2 mg/kg injected over 30 minutes exerts a negative inotropic action on the myocardium, and that this effect was particularly marked during infusion (Legrand et al., 1983). The negative inotropic effect is a possible explanation for the observed increase in heart rate. In order to compensate for a decrease in cardiac output a reflex increase in sympathetic tone and thereby increase in heart rate seems likely. Results of studies of the effect of intravenous administration of flecainide on heart rate in human patients have varied. Muhiddin *et al.* found that an intravenous administration of 2 mg/kg of flecainide caused a significant increase in heart rate with a maximum increase 10 minutes after infusion, and suggested a similar reflex mechanism as a result of decreased stroke volume (Muhiddin et al., 1985). Josephson *et al.* did not find any significant alteration in heart rate in patients with coronary artery disease using intravenous doses of flecainide 1 to 2 mg/kg (Josephson et al., 1985). In addition, Legrand *et al.* reported no significant change in heart rate after intravenous flecainide infusion (Legrand et al., 1983). An increase in heart rate after flecainide infusion in horses has not been reported in other studies and this aspect requires further investigation.

Regarding the efficacy of pharmacological conversion to sinus rhythm in the unconscious study, 5 mg/kg of NS8593 converted all horses in atrial fibrillation with an average time of 10.22 ± 1.87 minutes. In comparison, only one of two horses in atrial fibrillation converted to sinus rhythm

within 14.08 minutes when treated with 2 mg/kg of flecainide. From these findings, and because NS8593 is described to be atria-selective, it is reasonable to postulate that SK channels are present in equine hearts, and that the drug has even greater potential than flecainide in converting horses to sinus rhythm. However, it must be emphasized that these assumptions are based on a limited number of horses and additional studies are required.

In the present unconscious study only two horses were given flecainide; one horse was euthanized during the procedure as the procedure had to be terminated sooner than intended due to practical circumstances. Thus, the QTc results from those two horses were excluded from the study.

For the first time the effect of a negative modulator of SK channels, NS8593, is investigated in horses. Because NS8593 has the potential to cause convulsions, the horses were anaesthetized in correlation with drug investigation. In three of four horses receiving NS8593 convulsions were observed during or shortly after drug administration. Taking this into account NS8593 can be excluded as a potential antiarrhythmic drug in its present form. However, this drug is being investigated further and has opened up for atria-selective targeting as a new perspective in treating atrial fibrillation.

The unconscious study demonstrated that administration of 5 mg/kg of NS8593 did not have any significant effect on the QTc interval. These findings indicate that NS8593 appears atria-selective and that the compound has antiarrhythmic potential. From this, the results of the study support the findings of Diness *et al.*, who recently reported that inhibition of SK channels did not affect QT intervals in the tested concentration of NS8593 in rabbits, guinea-pigs and rats and thereby was found to be atria-selective (Diness et al., 2010).

A non-significant increase in heart rate was observed 20, 25 and 30 minutes after infusion of NS8593. However, to assess this observation further investigation of the action and metabolism of NS8593 in horses is required.

7. Conclusion

This thesis has reviewed the cardiac electrophysiology focusing on the ionic basis of the cardiac action potential as well as impulse conduction within the heart. Further, correlation between phases of the cardiac action potential and the surface electrocardiogram with special focus on the QT interval was reviewed. Also, an overview of atrial fibrillation in horses was provided as the thesis included a study in which a pacing-induced acute model for atrial fibrillation was used to evaluate the antiarrhythmic potential of NS8593 and flecainide actate. The study was divided into a conscious and an unconscious study.

In the present conscious study flecainide administered intravenously in the dosage of 2 mg/kg was able to restore sinus rhythm in all horses in atrial fibrillation without causing clinical adverse effects. Further, the results indicated that this antiarrhythmic drug has a significant prolonging effect on the QTc interval. However, in addition to a significant QTc prolongation a significant QRS prolongation was found. The observed QTc prolongation was therefore mainly the result of a QRS widening, a well-reported effect of flecainide. A prolongation of the JTc interval was found after flecainide infusion indicating that this drug affects the ventricular repolarization. However, the JTc interval prolongation was observed at higher heart rates and therefore likely explained by an over-correction due to Bazett's formula. Thus, these results support the fact that flecainide slows conduction velocity and has little effect on the ventricular repolarization phase. In view of the results of the present conscious study flecainide in the dosage of 2 mg/kg IV is a safe and effective antiarrhythmic drug for converting acute atrial fibrillation in horses.

Regarding the unconscious study, a negative modulator of SK channels was investigated in horses for the first time. The result demonstrated that 5 mg/kg of NS8593 was found to convert all horses in atrial fibrillation to sinus rhythm. Thus, SK channels are present in equine hearts and SK channel inhibition appears to be a promising new therapeutic target in the treatment of atrial fibrillation in horses. In addition, NS8593 did not have any significant effect on the QT interval in horses and therefore has decreased risk of ventricular proarrhythmia. Although NS8593 is excluded as a potential antiarrhythmic drug in its present form, the results of the unconscious study have revealed atria-selective targeting as a new perspective in treating atrial fibrillation in horses. However, additional studies are needed to clarify this aspect.

8. Perspectives

The project has several interesting perspectives and contributes interesting observations to be included in the research of equine cardiology.

The present study was a part of a PhD project; hence, the study was designed to evaluate other perspectives than QT interval changes on the electrocardiogram. This gave some difficulties in ECG interpretation. When pacing the paced P wave often coincided with the T wave leading to misinterpretation of the end of the T wave. In addition, in atrial fibrillation the overlap of atrial activity made it difficult to measure the terminal portion of the T wave and therefore an estimate was measured in such situations. Difficulties in determining the termination of the QT interval may also have affected the results of the study. Ideally, to improve the interpretation of the ECGs in QT measuring a study designed for QT measurements alone should be designed. In addition, it is considered essential that the ECGs are read by the same reader. However, regarding the timeframe available in this study the ECGs were read by two readers and on-screen markers were placed manually for QT interval measurements. This may have caused inter-observer variability in the measurements.

In the present study a control group was not included. Instead each horse was its own control. The optimum would have been a separate control group of horses going through the same procedures to be able to exclude time as a causal factor. However, this was not possible due limited personal as well as time-consuming and financial circumstances.

The small sample size used in this study is likewise a limitation with regard to the statistical analysis. Unfortunately, the timeframe available to this study was not sufficient for conducting a comprehensive validation regarding the sample size.

The most common correction method is the Bazett's equation. This method was also used in this study for calculating QTc intervals. However, Bazett's equation does not minimize the correlation sufficiently, particularly at higher heart rates. Therefore, accurate assessment of the QTc requires better correction methods and several methods are currently in development. An interesting future perspective would therefore be to correct the study data for heart rate using a more accurate method that does not over-correct the QTc intervals at higher heart rates.

Several interesting perspectives are beyond the scope of this thesis. As previously described, the atrial effective refractory period plays a crucial role in re-entry and a long atrial effective refractory

period increases the chance that a circulating impulse encounters refractory tissue and subsequently terminates. However, the SK channel inhibitory effect of NS8593 on the effective refractory period has not yet been investigated in horses. In this study the atrial effective refractory period was measured at different cycle lengths. Thus, future assessment of the measurements may reveal SK channels as a promising new therapeutic target in the treatment of atrial fibrillation in horses. Furthermore, little is known about the antiarrhythmic potential of flecainide acetate in horses as only few studies have investigated the antiarrhythmic potential of flecainide in equine cardiology. Thus, the effect of flecainide acetate on the effective refractory period has remained unanswered.

Atrial fibrillation is a disease that progresses over time. However, most animal models of atrial fibrillation for testing anti-atrial fibrillation compounds do not take this into account, which limits the translationability of the results obtained. In this study the efficacy of NS8593 for treating atrial fibrillation was studied in healthy horses with experimentally-induced atrial fibrillation. However, short-term rapid atrial pacing in horses with normal atria is likely to be different from natural atrial fibrillation in horses with remodeled or diseased atrial tissue. Therefore, future studies examining the efficacy and safety of NS8593 in horses with naturally-occuring atrial fibrillation, much like the clinical situation, will reveal the therapeutic potential for this class of compounds.

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Appendix A

Conscious study

Horse ID	Intervention	Time	QTn	QRSn	RRn-1	RRn-2	RRn-3	RRn-4	RRn-5	QTn	RRmod	RRmod	RRmod (mean)	HR	QTc (Bazetts)	QTc (Bazetts) (mean)	QRS (mean)	JT= (QTn-QRSn)	JT	JTc	JTc (mean)
			[msec]	[msec]	[msec]	[msec]	[msec]	[msec]	[msec]	[sec]	[msec]	[sec]	[sec]	[Bpm]	[msec]	[msec]	[msec]	[msec]	[sec]	[msec]	[msec]
8	Baseline standing	-5	568	118	1261	1251	1210	1648	1334	0,57	1299,90	1,30	1,70	35,36	498,19	438,03	130,00	450,00	0,45	394,69	337,46
8	Baseline standing	-5	580	132	1544	1261	1251	1210	1648	0,58	1435,10	1,44			484,16			448,00	0,45	373,97	
8	Baseline standing	-5	578	130	2550	1544	1261	1251	1210	0,58	1956,00	1,96			413,28			448,00	0,45	320,33	
8	Baseline standing	-5	524	140	2260	2550	1544	1261	1251	0,52	2045,60	2,05			366,37			384,00	0,38	268,49	
8	Baseline standing	-5	566	130	1520	2260	2550	1544	1261	0,57	1747,50	1,75			428,16			436,00	0,44	329,82	
8	Baseline standing	-4	604	138	2002	1716	1895	1663	1469	0,60	1846,90	1,85	1,79	33,54	444,44	425,95	125,60	466,00	0,47	342,90	331,84
8	Baseline standing	-4	588	116	1600	2002	1716	1895	1663	0,59	1727,80	1,73			447,33			472,00	0,47	359,08	
8	Baseline standing	-4	584	128	2407	1600	2002	1716	1895	0,58	2084,80	2,08			404,46			456,00	0,46	315,81	
8	Baseline standing	-4	524	124	1151	2407	1600	2002	1716	0,52	1588,70	1,59			415,73			400,00	0,40	317,35	
8	Baseline standing	-4	544	122	1729	1151	2407	1600	2002	0,54	1695,60	1,70			417,77			422,00	0,42	324,08	
8	Baseline standing	-3	574	124	3313	1277	1264	2096	1189	0,57	2366,80	2,37	1,85	32,37	373,11	434,01	123,20	450,00	0,45	292,50	342,18
8	Baseline standing	-3	564	118	2180	3313	1277	1264	2096	0,56	2216,30	2,22			378,85			446,00	0,45	299,59	
8	Baseline standing	-3	588	124	1172	2180	3313	1277	1264	0,59	1607,40	1,61			463,78			464,00	0,46	365,98	
8	Baseline standing	-3	588	128	1261	1172	2180	3313	1277	0,59	1541,90	1,54			473,53			460,00	0,46	370,45	
8	Baseline standing	-3	596	122	1236	1261	1172	2180	3313	0,60	1536,70	1,54			480,79			474,00	0,47	382,37	
8	Baseline standing	-2	594	134	1093	1531	1195	1396	1953	0,59	1307,10	1,31	1,21	49,50	519,56	546,62	132,40	460,00	0,46	402,35	426,11
8	Baseline standing	-2	640	128	985	1093	1531	1195	1396	0,64	1123,30	1,12			603,85			512,00	0,51	483,08	
8	Baseline standing	-2	606	138	1031	985	1093	1531	1195	0,61	1094,40	1,09			579,27			468,00	0,47	447,36	
8	Baseline standing	-2	598	130	1368	1031	985	1093	1531	0,60	1251,10	1,25			534,63			468,00	0,47	418,41	
8	Baseline standing	-2	562	132	1401	1368	1031	985	1093	0,56	1285,00	1,29			495,78			430,00	0,43	379,33	
8	Baseline standing	-1	542	144	1476	1824	1210	1234	1826	0,54	1529,80	1,53	1,39	43,05	438,21	485,78	132,00	398,00	0,40	321,78	374,03
8	Baseline standing	-1	600	128	1320	1476	1824	1210	1234	0,60	1382,00	1,38			510,38			472,00	0,47	401,50	
8	Baseline standing	-1	568	120	1116	1320	1476	1824	1210	0,57	1273,00	1,27			503,42			448,00	0,45	397,07	
8	Baseline standing	-1	580	122	1093	1116	1320	1476	1824	0,58	1231,70	1,23			522,61			458,00	0,46	412,68	
8	Baseline standing	-1	566	146	1885	1093	1116	1320	1476	0,57	1552,30	1,55			454,29			420,00	0,42	337,10	
8	Flecainide	1	632	144	1662	1401	1465	1298	1115	0,63	1499,00	1,50	1,40	42,71	516,20	531,09	138,80	488,00	0,49	398,58	413,89
8	Flecainide	1	624	122	1261	1662	1401	1465	1298	0,62	1379,30	1,38			531,32			502,00	0,50	427,44	
8	Flecainide	1	636	136	1443	1261	1662	1401	1465	0,64	1426,50	1,43			532,50			500,00	0,50	418,63	
8	Flecainide	1	622	126	1309	1443	1261	1662	1401	0,62	1375,50	1,38			530,35			496,00	0,50	422,91	
8	Flecainide	1	632	166	1292	1309	1443	1261	1662	0,63	1344,40	1,34			545,07			466,00	0,47	401,90	

Table 2

8	Flecainide	2	574	138	3986	1554	1413	1955	1351	0,57	2775,70	2,78	1,91	31,40	344,53	439,53	138,80	436,00	0,44	261,70	337,25
8	Flecainide	2	578	138	1301	3986	1554	1413	1955	0,58	1939,90	1,94			414,99			440,00	0,44	315,91	
8	Flecainide	2	620	134	1527	1301	3986	1554	1413	0,62	1719,00	1,72			472,88			486,00	0,49	370,68	
8	Flecainide	2	638	150	1220	1527	1301	3986	1554	0,64	1599,50	1,60			504,46			488,00	0,49	385,86	
8	Flecainide	2	568	134	1188	1220	1527	1301	3986	0,57	1519,40	1,52			460,80			434,00	0,43	352,09	
8	Flecainide	3	612	130	1633	1164	1355	1653	2070	0,61	1557,10	1,56	1,47	40,72	490,45	490,05	138,40	482,00	0,48	386,27	375,31
8	Flecainide	3	610	130	1977	1633	1164	1355	1653	0,61	1732,30	1,73			463,47			480,00	0,48	364,69	
8	Flecainide	3	584	136	1167	1977	1633	1164	1355	0,58	1394,10	1,39			494,61			448,00	0,45	379,43	
8	Flecainide	3	602	142	1240	1167	1977	1633	1164	0,60	1330,80	1,33			521,84			460,00	0,46	398,75	
8	Flecainide	3	558	154	1253	1240	1167	1977	1633	0,56	1352,20	1,35			479,86			404,00	0,40	347,42	
8	Flecainide	4	574	130	1834	1683	2357	1349	1073	0,57	1731,50	1,73	1,55	38,64	436,22	483,93	132,00	444,00	0,44	337,42	377,62
8	Flecainide	4	580	128	1493	1834	1683	2357	1349	0,58	1652,20	1,65			451,23			452,00	0,45	351,65	
8	Flecainide	4	638	134	1426	1493	1834	1683	2357	0,64	1599,00	1,60			504,54			504,00	0,50	398,57	
8	Flecainide	4	614	138	1249	1426	1493	1834	1683	0,61	1410,70	1,41			516,95			476,00	0,48	400,76	
8	Flecainide	4	598	130	1292	1249	1426	1493	1834	0,60	1371,10	1,37			510,70			468,00	0,47	399,68	
8	Flecainide	5	598	136	1671	1915	1367	1636	2096	0,60	1728,40	1,73	1,64	36,66	454,86	456,61	140,80	462,00	0,46	351,41	346,40
8	Flecainide	5	574	158	1647	1671	1915	1367	1636	0,57	1649,50	1,65			446,93			416,00	0,42	323,90	
8	Flecainide	5	580	134	1649	1647	1671	1915	1367	0,58	1649,20	1,65			451,64			446,00	0,45	347,29	
8	Flecainide	5	576	140	1223	1649	1647	1671	1915	0,58	1464,60	1,46			475,95			436,00	0,44	360,27	
8	Flecainide	5	590	136	1900	1223	1649	1647	1671	0,59	1691,30	1,69			453,67			454,00	0,45	349,10	
8	Flecainide	6	558	154	2856	2188	1287	1314	1269	0,56	2252,60	2,25	1,82	32,99	371,79	423,24	139,60	404,00	0,40	269,18	318,93
8	Flecainide	6	562	136	2070	2856	2188	1287	1314	0,56	2085,10	2,09			389,20			426,00	0,43	295,02	
8	Flecainide	6	598	126	1256	2070	2856	2188	1287	0,60	1675,10	1,68			462,04			472,00	0,47	364,69	
8	Flecainide	6	540	132	1221	1256	2070	2856	2188	0,54	1573,10	1,57			430,54			408,00	0,41	325,30	
8	Flecainide	6	568	150	1290	1221	1256	2070	2856	0,57	1507,40	1,51			462,63			418,00	0,42	340,46	
8	Flecainide	7	642	160	1538	1476	1456	1517	1391	0,64	1500,60	1,50	1,52	39,46	524,09	530,39	163,60	482,00	0,48	393,47	397,70
8	Flecainide	7	652	170	1516	1538	1476	1456	1517	0,65	1510,50	1,51			530,50			482,00	0,48	392,18	
8	Flecainide	7	664	164	1563	1516	1538	1476	1456	0,66	1531,70	1,53			536,51			500,00	0,50	404,00	
8	Flecainide	7	652	162	1524	1563	1516	1538	1476	0,65	1527,60	1,53			527,52			490,00	0,49	396,45	
8	Flecainide	7	660	162	1530	1524	1563	1516	1538	0,66	1531,50	1,53			533,32			498,00	0,50	402,41	
8	Flecainide	8	680	162	1620	1617	1588	1638	1573	0,68	1613,30	1,61	1,62	37,08	535,37	535,21	167,60	518,00	0,52	407,82	403,45
8	Flecainide	8	670	176	1590	1620	1617	1588	1638	0,67	1603,30	1,60			529,14			494,00	0,49	390,14	
8	Flecainide	8	688	172	1648	1590	1620	1617	1588	0,69	1624,50	1,62			539,79			516,00	0,52	404,85	
8	Flecainide	8	684	158	1593	1648	1590	1620	1617	0,68	1608,80	1,61			539,27			526,00	0,53	414,70	
8	Flecainide	8	682	170	1672	1593	1648	1590	1620	0,68	1640,40	1,64			532,49			512,00	0,51	399,76	
8	Flecainide	9	564	172	980	970	960	998	955	0,56	975,30	0,98	0,96	62,46	571,10	581,65	172,00	392,00	0,39	396,93	406,14
8	Flecainide	9	556	174	910	980	970	960	998	0,56	943,80	0,94			572,31			382,00	0,38	393,21	

Table 2 continued

8	Flecainide	9	590	172	953	910	980	970	960	0,59	949,50	0,95			605,49			418,00	0,42	428,97	
8	Flecainide	9	576	168	961	953	910	980	970	0,58	957,10	0,96			588,77			408,00	0,41	417,04	
8	Flecainide	9	564	174	1001	961	953	910	980	0,56	977,00	0,98			570,60			390,00	0,39	394,56	
8	Flecainide	10	648	166	1671	1619	1679	1586	1537	0,65	1639,50	1,64	1,64	36,51	506,08	497,38	158,80	482,00	0,48	376,44	373,50
8	Flecainide	10	632	160	1634	1671	1619	1679	1586	0,63	1639,60	1,64			493,57			472,00	0,47	368,62	
8	Flecainide	10	634	148	1622	1634	1671	1619	1679	0,63	1634,70	1,63			495,87			486,00	0,49	380,12	
8	Flecainide	10	616	154	1698	1622	1634	1671	1619	0,62	1665,80	1,67			477,28			462,00	0,46	357,96	
8	Flecainide	10	658	166	1612	1698	1622	1634	1671	0,66	1638,30	1,64			514,08			492,00	0,49	384,39	
8	Flecainide	11	626	154	1907	1708	1743	1928	1917	0,63	1853,90	1,85	1,81	33,21	459,76	467,60	152,80	472,00	0,47	346,66	353,93
8	Flecainide	11	620	142	1765	1907	1708	1743	1928	0,62	1801,80	1,80			461,89			478,00	0,48	356,10	
8	Flecainide	11	636	148	1725	1765	1907	1708	1743	0,64	1751,30	1,75			480,59			488,00	0,49	368,76	
8	Flecainide	11	636	158	1818	1725	1765	1907	1708	0,64	1792,00	1,79			475,10			478,00	0,48	357,07	
8	Flecainide	11	624	162	1863	1818	1725	1765	1907	0,62	1834,80	1,83			460,67			462,00	0,46	341,07	
8	Flecainide	12	500	146	1671	1671	1671	1473	1023	0,50	1586,40	1,59	1,47	40,73	396,98	448,92	152,40	354,00	0,35	281,06	323,00
8	Flecainide	12	526	156	1203	1671	1671	1671	1473	0,53	1417,20	1,42			441,85			370,00	0,37	310,80	
8	Flecainide	12	570	162	1172	1203	1671	1671	1671	0,57	1327,90	1,33			494,64			408,00	0,41	354,06	
8	Flecainide	12	568	164	1634	1172	1203	1671	1671	0,57	1505,90	1,51			462,86			404,00	0,40	329,22	
8	Flecainide	12	554	134	1592	1634	1172	1203	1671	0,55	1527,40	1,53			448,26			420,00	0,42	339,84	
8	Flecainide	13	628	132	1521	1503	1512	1534	1532	0,63	1518,90	1,52	1,56	38,43	509,56	504,21	133,60	496,00	0,50	402,45	397,27
8	Flecainide	13	612	142	1597	1521	1503	1512	1534	0,61	1557,60	1,56			490,37			470,00	0,47	376,59	
8	Flecainide	13	634	134	1578	1597	1521	1503	1512	0,63	1562,00	1,56			507,28			500,00	0,50	400,06	
8	Flecainide	13	634	128	1599	1578	1597	1521	1503	0,63	1577,20	1,58			504,83			506,00	0,51	402,91	
8	Flecainide	13	642	132	1603	1599	1578	1597	1521	0,64	1590,90	1,59			509,00			510,00	0,51	404,34	
9	Baseline standing	-5	550	132	2004	2024	2097	2145	2131	0,55	2044,10	2,04	2,10	28,56	384,69	384,20	134,80	418,00	0,42	292,36	291,19
9	Baseline standing	-5	568	138	2112	2004	2024	2097	2145	0,57	2083,40	2,08			393,52			430,00	0,43	297,91	
9	Baseline standing	-5	556	140	2194	2112	2004	2024	2097	0,56	2131,90	2,13			380,80			416,00	0,42	284,91	
9	Baseline standing	-5	554	134	2053	2194	2112	2004	2024	0,55	2079,30	2,08			384,19			420,00	0,42	291,27	
9	Baseline standing	-5	556	130	2248	2053	2194	2112	2004	0,56	2165,60	2,17			377,82			426,00	0,43	289,48	
9	Baseline standing	-4	550	130	1621	1157	1243	1166	2208	0,55	1503,60	1,50	1,43	41,91	448,54	465,98	130,00	420,00	0,42	342,52	357,06
9	Baseline standing	-4	546	124	1790	1621	1157	1243	1166	0,55	1575,80	1,58			434,95			422,00	0,42	336,17	
9	Baseline standing	-4	570	136	1122	1790	1621	1157	1243	0,57	1321,10	1,32			495,91			434,00	0,43	377,59	
9	Baseline standing	-4	562	128	1418	1122	1790	1621	1157	0,56	1390,20	1,39			476,65			434,00	0,43	368,09	
9	Baseline standing	-4	554	132	1260	1418	1122	1790	1621	0,55	1366,90	1,37			473,85			422,00	0,42	360,95	
9	Baseline standing	-3	598	122	1175	1090	1379	2364	1126	0,60	1292,40	1,29	1,52	39,60	526,02	465,12	129,20	476,00	0,48	418,71	359,52
9	Baseline standing	-3	574	134	1312	1175	1090	1379	2364	0,57	1374,30	1,37			489,63			440,00	0,44	375,33	
9	Baseline standing	-3	568	132	2255	1312	1175	1090	1379	0,57	1754,30	1,75			428,84			436,00	0,44	329,18	
9	Baseline standing	-3	532	124	1873	2255	1312	1175	1090	0,53	1745,20	1,75			402,71			408,00	0,41	308,84	

Table 2 continued

9	Baseline standing	-3	568	134	1122	1873	2255	1312	1175	0,57	1409,80	1,41			478,38			434,00	0,43	365,52	
9	Baseline standing	-2	576	142	2129	2178	2178	2106	2181	0,58	2146,60	2,15	2,11	28,42	393,14	392,33	140,00	434,00	0,43	296,22	295,97
9	Baseline standing	-2	572	140	2031	2129	2178	2178	2106	0,57	2087,50	2,09			395,90			432,00	0,43	299,00	
9	Baseline standing	-2	560	138	2113	2031	2129	2178	2178	0,56	2111,20	2,11			385,41			422,00	0,42	290,43	
9	Baseline standing	-2	570	144	2069	2113	2031	2129	2178	0,57	2090,90	2,09			394,19			426,00	0,43	294,61	
9	Baseline standing	-2	572	136	2154	2069	2113	2031	2129	0,57	2118,10	2,12			393,03			436,00	0,44	299,58	
9	Baseline standing	-1	572	140	1530	1531	1565	1552	1495	0,57	1532,40	1,53	1,55	38,59	462,07	460,98	139,60	432,00	0,43	348,98	349,02
9	Baseline standing	-1	568	142	1566	1530	1531	1565	1552	0,57	1553,80	1,55			455,67			426,00	0,43	341,75	
9	Baseline standing	-1	568	136	1573	1566	1530	1531	1565	0,57	1562,30	1,56			454,43			432,00	0,43	345,62	
9	Baseline standing	-1	568	138	1598	1573	1566	1530	1531	0,57	1576,30	1,58			452,41			430,00	0,43	342,49	
9	Baseline standing	-1	598	142	1527	1598	1573	1566	1530	0,60	1550,00	1,55			480,33			456,00	0,46	366,27	
9	Flecainide	1	514	138	2047	2127	2071	1979	2013	0,51	2055,20	2,06	2,11	28,40	358,54	351,50	138,40	376,00	0,38	262,28	256,26
9	Flecainide	1	506	138	2101	2047	2127	2071	1979	0,51	2077,60	2,08			351,05			368,00	0,37	255,31	
9	Flecainide	1	512	136	2215	2101	2047	2127	2071	0,51	2152,20	2,15			349,00			376,00	0,38	256,30	
9	Flecainide	1	516	140	2129	2215	2101	2047	2127	0,52	2135,00	2,14			353,14			376,00	0,38	257,33	
9	Flecainide	1	506	140	2159	2129	2215	2101	2047	0,51	2141,60	2,14			345,77			366,00	0,37	250,10	
9	Flecainide	2	538	136	2221	2266	2171	1915	1905	0,54	2162,80	2,16	2,22	27,07	365,83	368,32	138,40	402,00	0,40	273,35	275,36
9	Flecainide	2	544	138	2266	2221	2266	2171	1915	0,54	2212,40	2,21			365,74			406,00	0,41	272,96	
9	Flecainide	2	558	136	2231	2266	2221	2266	2171	0,56	2234,50	2,23			373,29			422,00	0,42	282,31	
9	Flecainide	2	552	136	2254	2231	2266	2221	2266	0,55	2248,50	2,25			368,12			416,00	0,42	277,43	
9	Flecainide	2	550	146	2207	2254	2231	2266	2221	0,55	2226,10	2,23			368,63			404,00	0,40	270,78	
9	Flecainide	3	572	148	1889	1925	1966	2046	2000	0,57	1930,70	1,93	1,98	30,34	411,66	410,19	140,80	424,00	0,42	305,15	310,04
9	Flecainide	3	570	142	1959	1889	1925	1966	2046	0,57	1951,00	1,95			408,08			428,00	0,43	306,42	
9	Flecainide	3	592	138	1998	1959	1889	1925	1966	0,59	1968,80	1,97			421,91			454,00	0,45	323,56	
9	Flecainide	3	568	136	2033	1998	1959	1889	1925	0,57	1993,40	1,99			402,30			432,00	0,43	305,98	
9	Flecainide	3	582	140	2107	2033	1998	1959	1889	0,58	2044,70	2,04			407,01			442,00	0,44	309,11	
9	Flecainide	4	628	140	2233	2198	2193	2177	1900	0,63	2183,10	2,18	2,23	26,85	425,03	407,84	141,60	488,00	0,49	330,28	313,12
9	Flecainide	4	622	142	2273	2233	2198	2193	2177	0,62	2239,90	2,24			415,60			480,00	0,48	320,72	
9	Flecainide	4	610	148	2245	2273	2233	2198	2193	0,61	2239,50	2,24			407,62			462,00	0,46	308,72	
9	Flecainide	4	590	138	2301	2245	2273	2233	2198	0,59	2269,90	2,27			391,61			452,00	0,45	300,01	
9	Flecainide	4	598	140	2214	2301	2245	2273	2233	0,60	2242,30	2,24			399,35			458,00	0,46	305,86	
9	Flecainide	5	620	142	2307	2191	2093	2256	2030	0,62	2229,60	2,23	2,15	27,94	415,22	416,01	146,40	478,00	0,48	320,12	316,08
9	Flecainide	5	600	146	2080	2307	2191	2093	2256	0,60	2155,40	2,16			408,68			454,00	0,45	309,24	
9	Flecainide	5	600	144	2126	2080	2307	2191	2093	0,60	2138,10	2,14			410,33			456,00	0,46	311,85	
9	Flecainide	5	618	158	2058	2126	2080	2307	2191	0,62	2112,00	2,11			425,25			460,00	0,46	316,53	
9	Flecainide	5	610	142	2082	2058	2126	2080	2307	0,61	2103,90	2,10			420,55			468,00	0,47	322,65	

Table 2 continued

9	Flecainide	6	648	140	2192	2236	2131	2037	2168	0,65	2176,80	2,18	2,21	27,10	439,20	437,13	146,00	508,00	0,51	344,31	339,01
9	Flecainide	6	648	144	2216	2192	2236	2131	2037	0,65	2186,80	2,19			438,20			504,00	0,50	340,82	
9	Flecainide	6	640	148	2255	2216	2192	2236	2131	0,64	2226,60	2,23			428,90			492,00	0,49	329,72	
9	Flecainide	6	658	148	2254	2255	2216	2192	2236	0,66	2242,40	2,24			439,41			510,00	0,51	340,58	
9	Flecainide	6	658	150	2240	2254	2255	2216	2192	0,66	2237,10	2,24			439,93			508,00	0,51	339,64	
9	Flecainide	7	576	140	2181	2156	2117	2056	2084	0,58	2147,40	2,15	2,20	27,30	393,07	392,83	154,40	436,00	0,44	297,53	288,70
9	Flecainide	7	574	166	2247	2181	2156	2117	2056	0,57	2192,60	2,19			387,64			408,00	0,41	275,54	
9	Flecainide	7	598	156	2228	2247	2181	2156	2117	0,60	2208,80	2,21			402,37			442,00	0,44	297,40	
9	Flecainide	7	572	164	2224	2228	2247	2181	2156	0,57	2216,00	2,22			384,25			408,00	0,41	274,08	
9	Flecainide	7	592	146	2230	2224	2228	2247	2181	0,59	2225,40	2,23			396,84			446,00	0,45	298,97	
9	Flecainide	8	590	166	1019	1042	1066	1063	931	0,59	1023,90	1,02	0,95	63,31	583,07	599,57	164,00	424,00	0,42	419,02	430,72
9	Flecainide	8	554	150	968	1019	1042	1066	1063	0,55	1004,90	1,00			552,65			404,00	0,40	403,01	
9	Flecainide	8	580	174	890	968	1019	1042	1066	0,58	951,30	0,95			594,66			406,00	0,41	416,26	
9	Flecainide	8	580	156	828	890	968	1019	1042	0,58	894,90	0,89			613,11			424,00	0,42	448,21	
9	Flecainide	8	608	174	820	828	890	968	1019	0,61	863,30	0,86			654,37			434,00	0,43	467,10	
9	Flecainide	9	540	148	970	970	980	1014	988	0,54	977,20	0,98	0,97	61,65	546,26	559,99	146,80	392,00	0,39	396,55	411,20
9	Flecainide	9	546	144	993	970	970	980	1014	0,55	986,90	0,99			549,61			402,00	0,40	404,66	
9	Flecainide	9	548	142	929	993	970	970	980	0,55	955,10	0,96			560,73			406,00	0,41	415,43	
9	Flecainide	9	570	146	960	929	993	970	970	0,57	959,10	0,96			582,03			424,00	0,42	432,95	
9	Flecainide	9	558	154	1014	960	929	993	970	0,56	988,20	0,99			561,32			404,00	0,40	406,40	
9	Flecainide	10	526	140	1277	1277	1277	1012	1007	0,53	1223,50	1,22	1,15	52,16	475,54	506,33	142,00	386,00	0,39	348,97	373,74
9	Flecainide	10	556	138	1035	1277	1277	1277	1012	0,56	1129,50	1,13			523,16			418,00	0,42	393,31	
9	Flecainide	10	522	142	1278	1035	1277	1277	1277	0,52	1229,10	1,23			470,84			380,00	0,38	342,76	
9	Flecainide	10	560	148	1017	1278	1035	1277	1277	0,56	1123,00	1,12			528,44			412,00	0,41	388,78	
9	Flecainide	10	546	142	1004	1004	1004	920	1516	0,55	1046,80	1,05			533,66			404,00	0,40	394,87	
9	Flecainide	11	594	140	1511	1135	1006	1006	1521	0,59	1335,80	1,34	1,36	44,24	513,94	491,48	139,60	454,00	0,45	392,81	371,29
9	Flecainide	11	554	136	1649	1511	1135	1006	1006	0,55	1441,40	1,44			461,44			418,00	0,42	348,16	
9	Flecainide	11	558	138	947	1649	1511	1135	1006	0,56	1168,50	1,17			516,20			420,00	0,42	388,54	
9	Flecainide	11	588	144	1450	947	1649	1511	1135	0,59	1343,90	1,34			507,22			444,00	0,44	383,00	
9	Flecainide	11	560	140	1581	1450	947	1649	1511	0,56	1491,20	1,49			458,59			420,00	0,42	343,94	
9	Flecainide	12	552	128	2069	2183	2031	1813	1978	0,55	2053,30	2,05	2,13	28,21	385,22	375,02	132,00	424,00	0,42	295,90	284,52
9	Flecainide	12	550	128	2162	2069	2183	2031	1813	0,55	2097,50	2,10			379,76			422,00	0,42	291,38	
9	Flecainide	12	542	134	2135	2162	2069	2183	2031	0,54	2128,20	2,13			371,53			408,00	0,41	279,68	
9	Flecainide	12	542	136	2242	2135	2162	2069	2183	0,54	2189,40	2,19			366,30			406,00	0,41	274,39	
9	Flecainide	12	548	134	2163	2242	2135	2162	2069	0,55	2166,50	2,17			372,31			414,00	0,41	281,27	
9	Flecainide	13	552	144	2199	2237	2190	2170	2078	0,55	2190,70	2,19	2,25	26,67	372,95	372,03	140,80	408,00	0,41	275,66	278,14

Table 2 continued

9	Flecainide	13	566	142	2387	2199	2237	2190	2170	0,57	2293,00	2,29			373,78			424,00	0,42	280,00	
9	Flecainide	13	558	144	2207	2387	2199	2237	2190	0,56	2243,50	2,24			372,54			414,00	0,41	276,40	
9	Flecainide	13	550	132	2289	2207	2387	2199	2237	0,55	2268,20	2,27			365,19			418,00	0,42	277,55	
9	Flecainide	13	564	142	2233	2289	2207	2387	2199	0,56	2253,60	2,25			375,70			422,00	0,42	281,11	
10	Baseline standing	-5	564	150	1813	1798	1755	1756	1674	0,56	1784,60	1,78	1,80	33,28	422,19	411,44	137,20	414,00	0,41	309,91	309,23
10	Baseline standing	-5	548	140	1759	1813	1798	1755	1756	0,55	1773,00	1,77			411,55			408,00	0,41	306,41	
10	Baseline standing	-5	552	136	1856	1759	1813	1798	1755	0,55	1816,40	1,82			409,57			416,00	0,42	308,67	
10	Baseline standing	-5	536	134	1840	1856	1759	1813	1798	0,54	1828,20	1,83			396,42			402,00	0,40	297,31	
10	Baseline standing	-5	562	126	1803	1840	1856	1759	1813	0,56	1812,30	1,81			417,47			436,00	0,44	323,87	
10	Baseline standing	-4	574	140	1550	1395	1406	1500	1652	0,57	1509,80	1,51	1,55	38,63	467,15	452,97	136,00	434,00	0,43	353,21	343,82
10	Baseline standing	-4	544	136	1541	1550	1395	1406	1500	0,54	1510,60	1,51			442,61			408,00	0,41	331,96	
10	Baseline standing	-4	564	126	1609	1541	1550	1395	1406	0,56	1547,80	1,55			453,34			438,00	0,44	352,06	
10	Baseline standing	-4	576	138	1618	1609	1541	1550	1395	0,58	1579,40	1,58			458,33			438,00	0,44	348,52	
10	Baseline standing	-4	564	140	1648	1618	1609	1541	1550	0,56	1617,60	1,62			443,45			424,00	0,42	333,37	
10	Baseline standing	-3	578	130	1836	2108	1854	1911	1862	0,58	1902,30	1,90	1,97	30,49	419,07	402,34	137,20	448,00	0,45	324,82	304,52
10	Baseline standing	-3	566	150	2069	1836	2108	1854	1911	0,57	1989,00	1,99			401,33			416,00	0,42	294,97	
10	Baseline standing	-3	558	132	1988	2069	1836	2108	1854	0,56	1987,60	1,99			395,79			426,00	0,43	302,17	
10	Baseline standing	-3	536	136	2091	1988	2069	1836	2108	0,54	2044,40	2,04			374,87			400,00	0,40	279,75	
10	Baseline standing	-3	582	138	1814	2091	1988	2069	1836	0,58	1914,50	1,91			420,63			444,00	0,44	320,89	
10	Baseline standing	-2	576	154	1937	2150	1864	2053	1929	0,58	1983,10	1,98	2,02	29,67	409,03	398,57	145,20	422,00	0,42	299,67	296,38
10	Baseline standing	-2	540	136	2245	1937	2150	1864	2053	0,54	2116,60	2,12			371,17			404,00	0,40	277,69	
10	Baseline standing	-2	572	152	1775	2245	1937	2150	1864	0,57	1931,60	1,93			411,56			420,00	0,42	302,20	
10	Baseline standing	-2	578	150	2236	1775	2245	1937	2150	0,58	2106,20	2,11			398,27			428,00	0,43	294,91	
10	Baseline standing	-2	566	134	1863	2236	1775	2245	1937	0,57	1974,40	1,97			402,81			432,00	0,43	307,44	
10	Baseline standing	-1	548	136	1880	1723	1792	1693	1741	0,55	1807,20	1,81	1,85	32,50	407,64	414,19	140,80	412,00	0,41	306,47	310,57
10	Baseline standing	-1	556	144	1838	1880	1723	1792	1693	0,56	1815,80	1,82			412,61			412,00	0,41	305,75	
10	Baseline standing	-1	570	156	1961	1838	1880	1723	1792	0,57	1887,60	1,89			414,88			414,00	0,41	301,33	
10	Baseline standing	-1	578	144	1834	1961	1838	1880	1723	0,58	1853,30	1,85			424,58			434,00	0,43	318,80	
10	Baseline standing	-1	562	124	1866	1834	1961	1838	1880	0,56	1867,70	1,87			411,23			438,00	0,44	320,49	
10	Flecainide	1	542	140	1951	1830	1822	1995	1873	0,54	1910,50	1,91	1,93	31,10	392,13	396,37	149,60	402,00	0,40	290,84	288,66
10	Flecainide	1	562	154	2108	1951	1830	1822	1995	0,56	2008,90	2,01			396,51			408,00	0,41	287,86	
10	Flecainide	1	562	146	1762	2108	1951	1830	1822	0,56	1862,90	1,86			411,76			416,00	0,42	304,79	
10	Flecainide	1	540	152	2029	1762	2108	1951	1830	0,54	1955,80	1,96			386,13			388,00	0,39	277,44	
10	Flecainide	1	546	156	1839	2029	1762	2108	1951	0,55	1907,40	1,91			395,34			390,00	0,39	282,39	
10	Flecainide	2	572	158	1766	1827	1845	1882	1967	0,57	1817,80	1,82	1,83	32,74	424,25	418,67	146,00	414,00	0,41	307,06	310,81
10	Flecainide	2	542	144	1845	1766	1827	1845	1882	0,54	1831,10	1,83			400,54			398,00	0,40	294,12	

Table 2 continued

10	Fecainide	2	556	144	1798	1845	1766	1827	1845	0,56	1811,80	1,81			413,07			412,00	0,41	306,09	
10	Flecainide	2	552	144	1914	1798	1845	1766	1827	0,55	1860,40	1,86			404,70			408,00	0,41	299,13	
10	Flecainide	2	612	140	1839	1914	1798	1845	1766	0,61	1843,20	1,84			450,78			472,00	0,47	347,66	
10	Flecainide	3	580	164	1780	1670	1630	1472	1414	0,58	1675,60	1,68	1,78	33,66	448,07	423,99	154,40	416,00	0,42	321,37	308,26
10	Flecainide	3	564	148	1752	1780	1670	1630	1472	0,56	1709,20	1,71			431,40			416,00	0,42	318,20	
10	Flecainide	3	552	150	1873	1752	1780	1670	1630	0,55	1794,90	1,79			412,02			402,00	0,40	300,06	
10	Flecainide	3	562	144	1892	1873	1752	1780	1670	0,56	1840,80	1,84			414,22			418,00	0,42	308,09	
10	Flecainide	3	570	166	1949	1892	1873	1752	1780	0,57	1893,40	1,89			414,24			404,00	0,40	293,60	
10	Flecainide	4	576	148	1760	1830	1894	1828	1853	0,58	1803,50	1,80	1,78	33,68	428,91	429,80	149,60	428,00	0,43	318,70	317,68
10	Flecainide	4	578	146	1835	1760	1830	1894	1828	0,58	1824,70	1,82			427,89			432,00	0,43	319,81	
10	Flecainide	4	556	144	1702	1835	1760	1830	1894	0,56	1766,40	1,77			418,34			412,00	0,41	309,99	
10	Flecainide	4	586	158	1707	1702	1835	1760	1830	0,59	1736,40	1,74			444,71			428,00	0,43	324,80	
10	Flecainide	4	572	152	1811	1707	1702	1835	1760	0,57	1776,60	1,78			429,14			420,00	0,42	315,10	
10	Flecainide	5	580	150	1902	1857	1765	1927	1738	0,58	1865,40	1,87	1,88	31,95	424,66	424,77	156,40	430,00	0,43	314,83	310,66
10	Flecainide	5	570	140	1790	1902	1857	1765	1927	0,57	1830,30	1,83			421,32			430,00	0,43	317,84	
10	Flecainide	5	592	162	1907	1790	1902	1857	1765	0,59	1863,90	1,86			433,62			430,00	0,43	314,96	
10	Flecainide	5	586	172	1915	1907	1790	1902	1857	0,59	1893,80	1,89			425,82			414,00	0,41	300,84	
10	Flecainide	5	582	158	1984	1915	1907	1790	1902	0,58	1934,90	1,93			418,40			424,00	0,42	304,82	
10	Flecainide	6	600	168	1967	1876	1856	1939	2076	0,60	1945,80	1,95	1,91	31,36	430,13	421,70	154,40	432,00	0,43	309,70	310,10
10	Flecainide	6	588	154	1890	1967	1876	1856	1939	0,59	1905,50	1,91			425,96			434,00	0,43	314,40	
10	Flecainide	6	592	156	1910	1890	1967	1876	1856	0,59	1902,90	1,90			429,15			436,00	0,44	316,07	
10	Flecainide	6	578	144	1788	1910	1890	1967	1876	0,58	1849,30	1,85			425,03			434,00	0,43	319,14	
10	Flecainide	6	558	150	2058	1788	1910	1890	1967	0,56	1963,30	1,96			398,24			408,00	0,41	291,18	
10	Flecainide	7	588	176	1804	1740	1850	1773	1746	0,59	1786,90	1,79	1,80	33,36	439,87	437,26	154,40	412,00	0,41	308,21	322,14
10	Flecainide	7	570	134	1724	1804	1740	1850	1773	0,57	1759,10	1,76			429,76			436,00	0,44	328,73	
10	Flecainide	7	598	154	1928	1724	1804	1740	1850	0,60	1848,20	1,85			439,87			444,00	0,44	326,59	
10	Flecainide	7	588	152	1775	1928	1724	1804	1740	0,59	1799,90	1,80			438,28			436,00	0,44	324,98	
10	Flecainide	7	588	156	1795	1775	1928	1724	1804	0,59	1798,10	1,80			438,50			432,00	0,43	322,16	
10	Flecainide	8	596	178	953	885	969	1081	975	0,60	956,00	0,96	0,97	61,69	609,56	587,84	172,00	418,00	0,42	427,51	413,40
10	Flecainide	8	584	172	1013	953	885	969	1081	0,58	990,60	0,99			586,76			412,00	0,41	413,95	
10	Flecainide	8	562	168	1035	1013	953	885	969	0,56	1000,80	1,00			561,78			394,00	0,39	393,84	
10	Flecainide	8	580	166	924	1035	1013	953	885	0,58	954,10	0,95			593,79			414,00	0,41	423,84	
10	Flecainide	8	576	176	954	924	1035	1013	953	0,58	961,90	0,96			587,30			400,00	0,40	407,84	
10	Flecainide	9	494	160	775	780	785	775	778	0,49	777,30	0,78	0,79	75,86	560,32	562,19	160,00	334,00	0,33	378,84	382,22
10	Flecainide	9	494	168	815	775	780	785	775	0,49	796,50	0,80			553,52			326,00	0,33	365,28	
10	Flecainide	9	504	172	775	815	775	780	785	0,50	784,50	0,78			569,03			332,00	0,33	374,84	

Table 2 continued

10	Flecainide	9	490	154	780	775	815	775	780	0,49	782,00	0,78			554,11			336,00	0,34	379,96	
10	Flecainide	9	518	146	844	780	775	815	775	0,52	814,50	0,81			573,96			372,00	0,37	412,19	
10	Flecainide	10	596	148	978	988	981	981	982	0,60	981,00	0,98	0,98	61,13	601,74	611,66	155,60	448,00	0,45	452,32	454,61
10	Flecainide	10	602	154	982	978	988	981	981	0,60	981,60	0,98			607,62			448,00	0,45	452,18	
10	Flecainide	10	612	158	982	982	978	988	981	0,61	982,10	0,98			617,55			454,00	0,45	458,12	
10	Flecainide	10	606	160	979	982	982	978	988	0,61	980,70	0,98			611,93			446,00	0,45	450,37	
10	Flecainide	10	614	158	985	979	982	982	978	0,61	982,50	0,98			619,44			456,00	0,46	460,04	
10	Flecainide	11	598	134	974	967	983	1003	979	0,60	976,90	0,98	0,98	61,28	605,03	594,62	141,60	464,00	0,46	469,45	451,53
10	Flecainide	11	604	148	981	974	967	983	1003	0,60	980,60	0,98			609,95			456,00	0,46	460,49	
10	Flecainide	11	570	138	979	981	974	967	983	0,57	978,10	0,98			576,35			432,00	0,43	436,81	
10	Flecainide	11	576	140	982	979	981	974	967	0,58	979,00	0,98			582,14			436,00	0,44	440,65	
10	Flecainide	11	594	148	983	982	979	981	974	0,59	981,30	0,98			599,63			446,00	0,45	450,23	
10	Flecainide	12	570	158	2057	1884	1919	1938	1821	0,57	1973,10	1,97	1,96	30,67	405,79	412,72	147,20	412,00	0,41	293,31	307,51
10	Flecainide	12	578	142	1891	2057	1884	1919	1938	0,58	1931,00	1,93			415,95			436,00	0,44	313,76	
10	Flecainide	12	576	138	1875	1891	2057	1884	1919	0,58	1901,70	1,90			417,69			438,00	0,44	317,62	
10	Flecainide	12	576	138	2013	1875	1891	2057	1884	0,58	1964,70	1,96			410,94			438,00	0,44	312,48	
10	Flecainide	12	586	160	2052	2013	1875	1891	2057	0,59	2010,90	2,01			413,24			426,00	0,43	300,41	
10	Flecainide	13	586	138	1894	1846	1790	1893	1777	0,59	1862,20	1,86	1,91	31,46	429,42	415,46	143,60	448,00	0,45	328,30	311,49
10	Flecainide	13	582	134	1891	1894	1846	1790	1893	0,58	1877,20	1,88			424,78			448,00	0,45	326,98	
10	Flecainide	13	572	148	1969	1891	1894	1846	1790	0,57	1915,70	1,92			413,27			424,00	0,42	306,34	
10	Flecainide	13	562	144	2014	1969	1891	1894	1846	0,56	1963,90	1,96			401,03			418,00	0,42	298,27	
10	Flecainide	13	566	154	1878	2014	1969	1891	1894	0,57	1917,20	1,92			408,77			412,00	0,41	297,55	
11	Baseline standing	-5	572	140	1183	1625	1285	1132	2094	0,57	1367,60	1,37	1,38	43,63	489,12	492,55	139,60	432,00	0,43	369,41	373,16
11	Baseline standing	-5	566	136	1199	1183	1625	1285	1132	0,57	1240,30	1,24			508,22			430,00	0,43	386,10	
11	Baseline standing	-5	586	136	1096	1199	1183	1625	1285	0,59	1197,10	1,20			535,59			450,00	0,45	411,29	
11	Baseline standing	-5	590	146	1814	1096	1199	1183	1625	0,59	1526,90	1,53			477,47			444,00	0,44	359,32	
11	Baseline standing	-5	562	140	1666	1814	1096	1199	1183	0,56	1543,60	1,54			452,34			422,00	0,42	339,66	
11	Baseline standing	-4	562	144	1284	938	1972	993	1138	0,56	1239,90	1,24	1,37	43,70	504,71	480,11	141,20	418,00	0,42	375,39	359,13
11	Baseline standing	-4	566	134	1514	1284	938	1972	993	0,57	1404,10	1,40			477,66			432,00	0,43	364,57	
11	Baseline standing	-4	552	136	1752	1514	1284	938	1972	0,55	1598,20	1,60			436,64			416,00	0,42	329,06	
11	Baseline standing	-4	570	144	1144	1752	1514	1284	938	0,57	1296,00	1,30			500,69			426,00	0,43	374,20	
11	Baseline standing	-4	554	148	1287	1144	1752	1514	1284	0,55	1327,30	1,33			480,87			406,00	0,41	352,40	
11	Baseline standing	-3	576	140	1302	1042	1613	1477	1137	0,58	1282,10	1,28	1,50	39,88	508,70	478,77	145,20	436,00	0,44	385,06	359,42
11	Baseline standing	-3	546	156	2694	1302	1042	1613	1477	0,55	2020,60	2,02			384,11			390,00	0,39	274,36	
11	Baseline standing	-3	596	150	1351	2694	1302	1042	1613	0,60	1610,00	1,61			469,71			446,00	0,45	351,50	
11	Baseline standing	-3	592	142	1128	1351	2694	1302	1042	0,59	1338,00	1,34			511,79			450,00	0,45	389,03	

Table 2 continued

11	Baseline standing	-3	586	138	1024	1128	1351	2694	1302	0,59	1272,30	1,27			519,52			448,00	0,45	397,18	
11	Baseline standing	-2	584	142	1254	932	1737	1620	1529	0,58	1302,00	1,30	1,37	43,65	511,81	496,88	145,20	442,00	0,44	387,36	372,62
11	Baseline standing	-2	600	148	1258	1254	932	1737	1620	0,60	1308,70	1,31			524,48			452,00	0,45	395,11	
11	Baseline standing	-2	562	154	1270	1258	1254	932	1737	0,56	1278,90	1,28			496,96			408,00	0,41	360,78	
11	Baseline standing	-2	572	148	2107	1270	1258	1254	932	0,57	1651,90	1,65			445,05			424,00	0,42	329,89	
11	Baseline standing	-2	584	134	1064	2107	1270	1258	1254	0,58	1331,60	1,33			506,09			450,00	0,45	389,96	
11	Baseline standing	-1	586	146	1088	886	841	1026	3530	0,59	1260,90	1,26	1,25	47,89	521,86	517,58	146,00	440,00	0,44	391,84	387,15
11	Baseline standing	-1	564	144	1537	1088	886	841	1026	0,56	1261,40	1,26			502,17			420,00	0,42	373,96	
11	Baseline standing	-1	596	142	1242	1537	1088	886	841	0,60	1209,90	1,21			541,84			454,00	0,45	412,74	
11	Baseline standing	-1	564	150	1355	1242	1537	1088	886	0,56	1277,00	1,28			499,10			414,00	0,41	366,36	
11	Baseline standing	-1	586	148	1196	1355	1242	1537	1088	0,59	1255,70	1,26			522,94			438,00	0,44	390,87	
11	Flecainide	1	472	140	1180	1230	2172	1248	1004	0,47	1278,40	1,28	1,37	43,70	417,45	422,33	140,80	332,00	0,33	293,63	301,87
11	Flecainide	1	540	140	1558	1180	1230	2172	1248	0,54	1480,00	1,48			443,88			400,00	0,40	328,80	
11	Flecainide	1	484	140	1528	1558	1180	1230	2172	0,48	1533,80	1,53			390,81			344,00	0,34	277,76	
11	Flecainide	1	470	146	1250	1528	1558	1180	1230	0,47	1327,40	1,33			407,94			324,00	0,32	281,22	
11	Flecainide	1	504	138	1138	1250	1528	1558	1180	0,50	1245,60	1,25			451,59			366,00	0,37	327,94	
11	Flecainide	2	514	144	1128	1058	1811	1340	1352	0,51	1225,90	1,23	1,56	38,45	464,23	418,89	145,60	370,00	0,37	334,18	299,94
11	Flecainide	2	478	148	1528	1128	1058	1811	1340	0,48	1410,50	1,41			402,48			330,00	0,33	277,86	
11	Flecainide	2	514	142	1454	1528	1128	1058	1811	0,51	1432,30	1,43			429,48			372,00	0,37	310,83	
11	Flecainide	2	540	150	1442	1454	1528	1128	1058	0,54	1383,20	1,38			459,15			390,00	0,39	331,61	
11	Flecainide	2	520	144	3304	1442	1454	1528	1128	0,52	2351,40	2,35			339,11			376,00	0,38	245,20	
11	Flecainide	3	524	146	1084	1480	1297	1142	1086	0,52	1190,50	1,19	1,52	39,45	480,25	407,63	144,40	378,00	0,38	346,44	289,47
11	Flecainide	3	492	146	1676	1084	1480	1297	1142	0,49	1446,70	1,45			409,05			346,00	0,35	287,66	
11	Flecainide	3	514	148	1500	1676	1084	1480	1297	0,51	1471,30	1,47			423,75			366,00	0,37	301,74	
11	Flecainide	3	476	144	1870	1500	1676	1084	1480	0,48	1659,00	1,66			369,56			332,00	0,33	257,76	
11	Flecainide	3	482	138	2076	1870	1500	1676	1084	0,48	1838,00	1,84			355,53			344,00	0,34	253,74	
11	Flecainide	4	594	144	1308	1302	1346	1388	1388	0,59	1326,60	1,33	1,30	46,14	515,72	532,22	143,20	450,00	0,45	390,70	406,64
11	Flecainide	4	596	142	1289	1308	1302	1346	1388	0,60	1309,70	1,31			520,79			454,00	0,45	396,71	
11	Flecainide	4	612	146	1290	1289	1308	1302	1346	0,61	1298,40	1,30			537,09			466,00	0,47	408,96	
11	Flecainide	4	618	140	1266	1290	1289	1308	1302	0,62	1280,90	1,28			546,05			478,00	0,48	422,35	
11	Flecainide	4	614	144	1288	1266	1290	1289	1308	0,61	1285,90	1,29			541,46			470,00	0,47	414,47	
11	Flecainide	5	626	152	1466	1452	1474	1440	1438	0,63	1458,60	1,46	1,47	40,68	518,33	512,52	148,80	474,00	0,47	392,47	389,98
11	Flecainide	5	618	150	1502	1466	1452	1474	1440	0,62	1480,80	1,48			507,86			468,00	0,47	384,59	
11	Flecainide	5	622	148	1466	1502	1466	1452	1474	0,62	1472,60	1,47			512,56			474,00	0,47	390,60	
11	Flecainide	5	622	146	1498	1466	1502	1466	1452	0,62	1484,20	1,48			510,56			476,00	0,48	390,72	
11	Flecainide	5	624	148	1470	1498	1466	1502	1466	0,62	1478,00	1,48			513,27			476,00	0,48	391,53	

Table 2 continued

11	Flecainide	6	640	150	1499	1495	1501	1510	1487	0,64	1498,30	1,50	1,47	40,83	522,85	528,71	150,00	490,00	0,49	400,31	404,96
11	Flecainide	6	646	150	1461	1499	1495	1501	1510	0,65	1480,90	1,48			530,85			496,00	0,50	407,59	
11	Flecainide	6	630	154	1481	1461	1499	1495	1501	0,63	1482,20	1,48			517,47			476,00	0,48	390,98	
11	Flecainide	6	646	150	1441	1481	1461	1499	1495	0,65	1462,20	1,46			534,23			496,00	0,50	410,18	
11	Flecainide	6	642	146	1382	1441	1481	1461	1499	0,64	1423,30	1,42			538,13			496,00	0,50	415,75	
11	Flecainide	7	654	154	1426	1467	1416	1452	1471	0,65	1440,30	1,44	1,41	42,47	544,94	548,24	155,20	500,00	0,50	416,62	417,66
11	Flecainide	7	654	158	1420	1426	1467	1416	1452	0,65	1428,70	1,43			547,15			496,00	0,50	414,96	
11	Flecainide	7	642	152	1391	1420	1426	1467	1416	0,64	1410,40	1,41			540,58			490,00	0,49	412,60	
11	Flecainide	7	650	156	1372	1391	1420	1426	1467	0,65	1395,50	1,40			550,24			494,00	0,49	418,18	
11	Flecainide	7	658	156	1382	1372	1391	1420	1426	0,66	1389,10	1,39			558,29			502,00	0,50	425,93	
11	Flecainide	8	636	160	1404	1370	1378	1404	1378	0,64	1392,00	1,39	1,39	43,05	539,06	537,38	160,80	476,00	0,48	403,45	401,18
11	Flecainide	8	638	160	1366	1404	1370	1378	1404	0,64	1379,00	1,38			543,30			478,00	0,48	407,05	
11	Flecainide	8	640	160	1418	1366	1404	1370	1378	0,64	1397,40	1,40			541,40			480,00	0,48	406,05	
11	Flecainide	8	626	164	1394	1418	1366	1404	1370	0,63	1394,60	1,39			530,09			462,00	0,46	391,22	
11	Flecainide	8	632	160	1416	1394	1418	1366	1404	0,63	1405,60	1,41			533,07			472,00	0,47	398,12	
11	Flecainide	9	650	158	1453	1477	1474	1470	1473	0,65	1463,60	1,46	1,47	40,74	537,28	536,27	160,40	492,00	0,49	406,68	404,10
11	Flecainide	9	664	160	1491	1453	1477	1474	1470	0,66	1478,20	1,48			546,14			504,00	0,50	414,54	
11	Flecainide	9	644	164	1468	1491	1453	1477	1474	0,64	1472,60	1,47			530,69			480,00	0,48	395,55	
11	Flecainide	9	650	162	1474	1468	1491	1453	1477	0,65	1472,70	1,47			535,62			488,00	0,49	402,13	
11	Flecainide	9	646	158	1481	1474	1468	1491	1453	0,65	1476,50	1,48			531,64			488,00	0,49	401,61	
11	Flecainide	10	488	164	1012	998	988	979	933	0,49	995,60	1,00	0,97	61,63	489,08	502,35	162,00	324,00	0,32	324,72	338,16
11	Flecainide	10	490	162	958	1012	998	988	979	0,49	977,90	0,98			495,51			328,00	0,33	331,69	
11	Flecainide	10	498	164	953	958	1012	998	988	0,50	967,90	0,97			506,19			334,00	0,33	339,49	
11	Flecainide	10	492	160	951	953	958	1012	998	0,49	962,90	0,96			501,39			332,00	0,33	338,34	
11	Flecainide	10	510	160	962	951	953	958	1012	0,51	963,50	0,96			519,57			350,00	0,35	356,57	
11	Flecainide	11	482	148	990	966	942	967	999	0,48	979,00	0,98	0,98	61,22	487,14	487,30	153,60	334,00	0,33	337,56	332,14
11	Flecainide	11	480	158	1018	990	966	942	967	0,48	994,50	0,99			481,33			322,00	0,32	322,89	
11	Flecainide	11	478	152	981	1018	990	966	942	0,48	983,90	0,98			481,89			326,00	0,33	328,66	
11	Flecainide	11	484	156	943	981	1018	990	966	0,48	965,10	0,97			492,67			328,00	0,33	333,88	
11	Flecainide	11	488	154	981	943	981	1018	990	0,49	978,00	0,98			493,46			334,00	0,33	337,74	
11	Flecainide	12	498	152	1323	1340	1513	1294	1315	0,50	1341,70	1,34	1,36	44,03	429,93	432,78	150,00	346,00	0,35	298,71	304,27
11	Flecainide	12	498	148	1368	1323	1340	1513	1294	0,50	1363,30	1,36			426,51			350,00	0,35	299,76	
11	Flecainide	12	510	150	1386	1368	1323	1340	1513	0,51	1384,20	1,38			433,48			360,00	0,36	305,99	
11	Flecainide	12	510	148	1382	1386	1368	1323	1340	0,51	1371,30	1,37			435,52			362,00	0,36	309,13	
11	Flecainide	12	510	152	1338	1382	1386	1368	1323	0,51	1353,10	1,35			438,44			358,00	0,36	307,76	
11	Flecainide	13	470	142	2606	1031	1125	1112	1357	0,47	1868,60	1,87	1,54	38,99	343,83	391,20	142,80	328,00	0,33	239,95	275,03

Table 2 continued

11	Flecainide	13	470	146	1115	2606	1031	1125	1112	0,47	1405,50	1,41			396,44			324,00	0,32	273,29	
11	Flecainide	13	498	140	1191	1115	2606	1031	1125	0,50	1294,70	1,29			437,67			358,00	0,36	314,63	
11	Flecainide	13	488	136	1115	1191	1115	2606	1031	0,49	1270,90	1,27			432,88			352,00	0,35	312,24	
11	Flecainide	13	470	150	2279	1115	1191	1115	2606	0,47	1853,70	1,85			345,21			320,00	0,32	235,03	
12	Baseline standing	-5	536	160	954	1128	3408	1295	1833	0,54	1356,20	1,36	1,68	35,69	460,26	422,10	161,20	376,00	0,38	322,87	295,30
12	Baseline standing	-5	542	156	1249	954	1128	3408	1295	0,54	1398,40	1,40			458,34			386,00	0,39	326,42	
12	Baseline standing	-5	510	154	3263	1249	954	1128	3408	0,51	2430,30	2,43			327,14			356,00	0,36	228,36	
12	Baseline standing	-5	540	164	853	3263	1249	954	1128	0,54	1412,20	1,41			454,41			376,00	0,38	316,40	
12	Baseline standing	-5	552	172	2185	853	3263	1249	954	0,55	1809,70	1,81			410,33			380,00	0,38	282,48	
12	Baseline standing	-4	556	156	1461	1212	1577	2786	1152	0,56	1524,40	1,52	1,18	50,77	450,32	517,92	156,80	400,00	0,40	323,97	372,11
12	Baseline standing	-4	574	160	908	1461	1212	1577	2786	0,57	1303,70	1,30			502,72			414,00	0,41	362,59	
12	Baseline standing	-4	551	158	998	908	1461	1212	1577	0,55	1105,60	1,11			524,03			393,00	0,39	373,76	
12	Baseline standing	-4	548	152	722	998	908	1461	1212	0,55	918,70	0,92			571,73			396,00	0,40	413,15	
12	Baseline standing	-4	556	158	1152	722	998	908	1461	0,56	1057,10	1,06			540,78			398,00	0,40	387,10	
12	Baseline standing	-3	546	168	1206	823	3958	1038	1036	0,55	1370,80	1,37	1,73	34,67	466,34	426,68	158,00	378,00	0,38	322,85	303,74
12	Baseline standing	-3	562	154	1114	1206	823	3958	1038	0,56	1380,10	1,38			478,39			408,00	0,41	347,30	
12	Baseline standing	-3	566	158	1371	1114	1206	823	3958	0,57	1507,00	1,51			461,06			408,00	0,41	332,36	
12	Baseline standing	-3	490	152	3915	1371	1114	1206	823	0,49	2546,00	2,55			307,09			338,00	0,34	211,83	
12	Baseline standing	-3	572	158	1396	3915	1371	1114	1206	0,57	1850,10	1,85			420,53			414,00	0,41	304,37	
12	Baseline standing	-2	558	166	1163	3432	958	797	822	0,56	1525,60	1,53	1,62	36,96	451,77	435,95	157,20	392,00	0,39	317,37	311,81
12	Baseline standing	-2	552	152	1370	1163	3432	958	797	0,55	1436,30	1,44			460,59			400,00	0,40	333,76	
12	Baseline standing	-2	548	158	1398	1370	1163	3432	958	0,55	1528,30	1,53			443,28			390,00	0,39	315,47	
12	Baseline standing	-2	554	154	1390	1398	1370	1163	3432	0,55	1571,10	1,57			441,99			400,00	0,40	319,12	
12	Baseline standing	-2	548	156	2771	1390	1398	1370	1163	0,55	2056,60	2,06			382,13			392,00	0,39	273,35	
12	Baseline standing	-1	554	160	1007	1431	1420	827	871	0,55	1101,50	1,10	1,06	56,36	527,86	507,86	165,20	394,00	0,39	375,41	347,60
12	Baseline standing	-1	506	164	788	1007	1431	1420	827	0,51	963,20	0,96			515,58			342,00	0,34	348,47	
12	Baseline standing	-1	510	166	1064	788	1007	1431	1420	0,51	1075,40	1,08			491,80			344,00	0,34	331,72	
12	Baseline standing	-1	518	172	1206	1064	788	1007	1431	0,52	1138,40	1,14			485,49			346,00	0,35	324,29	
12	Baseline standing	-1	530	164	1035	1206	1064	788	1007	0,53	1044,60	1,04			518,56			366,00	0,37	358,10	
12	Flecainide	1	496	154	752	816	904	1012	828	0,50	813,60	0,81	0,90	66,63	549,89	515,70	156,00	342,00	0,34	379,16	350,82
12	Flecainide	1	498	154	1006	752	816	904	1012	0,50	926,60	0,93			517,35			344,00	0,34	357,37	
12	Flecainide	1	514	160	958	1006	752	816	904	0,51	927,40	0,93			533,74			354,00	0,35	367,60	
12	Flecainide	1	464	158	730	958	1006	752	816	0,46	814,00	0,81			514,29			306,00	0,31	339,16	
12	Flecainide	1	468	154	1206	730	958	1006	752	0,47	1020,60	1,02			463,25			314,00	0,31	310,81	
12	Flecainide	2	510	162	877	1124	3120	1070	1428	0,51	1225,10	1,23	2,17	27,66	460,77	358,40	154,00	348,00	0,35	314,41	248,89
12	Flecainide	2	462	150	4056	877	1124	3120	1070	0,46	2734,80	2,73			279,37			312,00	0,31	188,67	

Table 2 continued

12	Flecainide	2	498	154	2138	4056	877	1124	3120	0,50	2392,30	2,39			321,97			344,00	0,34	222,41	
12	Flecainide	2	532	148	942	2138	4056	877	1124	0,53	1504,30	1,50			433,75			384,00	0,38	313,09	
12	Flecainide	2	512	156	4188	942	2138	4056	877	0,51	2989,50	2,99			296,12			356,00	0,36	205,90	
12	Flecainide	3	564	162	1132	826	2690	1498	1912	0,56	1341,20	1,34	1,70	35,37	487,00	433,56	159,60	402,00	0,40	347,12	305,96
12	Flecainide	3	522	160	4230	1132	826	2690	1498	0,52	2842,80	2,84			309,60			362,00	0,36	214,70	
12	Flecainide	3	564	160	1078	4230	1132	826	2690	0,56	1849,80	1,85			414,68			404,00	0,40	297,04	
12	Flecainide	3	522	164	824	1078	4230	1132	826	0,52	1246,40	1,25			467,56			358,00	0,36	320,67	
12	Flecainide	3	536	152	786	824	1078	4230	1132	0,54	1201,80	1,20			488,93			384,00	0,38	350,28	
12	Flecainide	4	526	156	1024	1196	2706	744	1266	0,53	1222,80	1,22	1,72	34,81	475,67	412,63	158,80	370,00	0,37	334,60	288,81
12	Flecainide	4	510	166	2770	1024	1196	2706	744	0,51	2054,40	2,05			355,82			344,00	0,34	240,00	
12	Flecainide	4	532	158	1128	2770	1024	1196	2706	0,53	1610,60	1,61			419,20			374,00	0,37	294,70	
12	Flecainide	4	570	162	1268	1128	2770	1024	1196	0,57	1358,60	1,36			489,02			408,00	0,41	350,04	
12	Flecainide	4	498	152	3250	1268	1128	2770	1024	0,50	2370,80	2,37			323,43			346,00	0,35	224,71	
12	Flecainide	5	548	158	910	654	972	1742	786	0,55	935,80	0,94	1,01	59,14	566,49	520,55	157,20	390,00	0,39	403,16	364,08
12	Flecainide	5	516	160	1118	910	654	972	1742	0,52	1077,80	1,08			497,03			356,00	0,36	342,91	
12	Flecainide	5	514	154	1183	1118	910	654	972	0,51	1068,70	1,07			497,20			360,00	0,36	348,24	
12	Flecainide	5	512	156	774	1183	1118	910	654	0,51	891,80	0,89			542,17			356,00	0,36	376,98	
12	Flecainide	5	524	158	1246	774	1183	1118	910	0,52	1098,90	1,10			499,86			366,00	0,37	349,14	
12	Flecainide	6	584	156	1579	1609	1595	1552	1538	0,58	1579,80	1,58	1,53	39,34	464,63	476,58	152,80	428,00	0,43	340,52	352,84
12	Flecainide	6	592	154	1544	1579	1609	1595	1552	0,59	1563,40	1,56			473,46			438,00	0,44	350,30	
12	Flecainide	6	592	150	1481	1544	1579	1609	1595	0,59	1527,60	1,53			478,98			442,00	0,44	357,62	
12	Flecainide	6	590	154	1460	1481	1544	1579	1609	0,59	1499,40	1,50			481,83			436,00	0,44	356,06	
12	Flecainide	6	584	150	1407	1460	1481	1544	1579	0,58	1455,90	1,46			484,00			434,00	0,43	359,69	
12	Flecainide	7	578	162	1357	1367	1395	1400	1450	0,58	1376,40	1,38	1,33	45,04	492,67	509,24	161,60	416,00	0,42	354,59	369,20
12	Flecainide	7	592	162	1327	1357	1367	1395	1400	0,59	1351,10	1,35			509,31			430,00	0,43	369,93	
12	Flecainide	7	586	158	1298	1327	1357	1367	1395	0,59	1326,30	1,33			508,83			428,00	0,43	371,64	
12	Flecainide	7	588	164	1289	1298	1327	1357	1367	0,59	1309,20	1,31			513,89			424,00	0,42	370,56	
12	Flecainide	7	594	162	1283	1289	1298	1327	1357	0,59	1297,50	1,30			521,47			432,00	0,43	379,25	
12	Flecainide	8	574	164	938	981	981	981	981	0,57	959,50	0,96	0,97	61,86	585,99	580,08	160,00	410,00	0,41	418,56	417,59
12	Flecainide	8	566	158	1032	938	981	981	981	0,57	997,90	1,00			566,60			408,00	0,41	408,43	
12	Flecainide	8	572	156	962	986	953	953	953	0,57	964,10	0,96			582,55			416,00	0,42	423,67	
12	Flecainide	8	566	162	956	998	998	998	962	0,57	973,40	0,97			573,68			404,00	0,40	409,48	
12	Flecainide	8	578	160	928	956	998	998	998	0,58	954,60	0,95			591,58			418,00	0,42	427,82	
12	Flecainide	9	508	166	804	786	780	778	784	0,51	793,40	0,79	0,79	75,96	570,32	581,15	163,60	342,00	0,34	383,95	397,03
12	Flecainide	9	528	166	860	804	786	780	778	0,53	825,20	0,83			581,24			362,00	0,36	398,50	
12	Flecainide	9	512	164	741	741	778	778	808	0,51	755,10	0,76			589,21			348,00	0,35	400,48	

Table 2 continued

12	Flecainide	9	520	160	818	741	741	778	778	0,52	786,90	0,79			586,20			360,00	0,36	405,83	
12	Flecainide	9	514	162	798	818	741	741	778	0,51	788,60	0,79			578,81			352,00	0,35	396,38	
12	Flecainide	10	604	164	996	733	733	1014	972	0,60	916,50	0,92	0,85	70,70	630,91	650,40	164,40	440,00	0,44	459,61	470,76
12	Flecainide	10	596	168	984	996	733	733	1014	0,60	939,20	0,94			614,99			428,00	0,43	441,64	
12	Flecainide	10	606	162	1030	984	996	733	733	0,61	958,00	0,96			619,14			444,00	0,44	453,63	
12	Flecainide	10	576	164	667	667	667	1030	984	0,58	735,00	0,74			671,86			412,00	0,41	480,57	
12	Flecainide	10	596	164	706	706	668	668	668	0,60	694,60	0,69			715,12			432,00	0,43	518,34	
12	Flecainide	11	586	162	1669	1654	1677	1693	1631	0,59	1665,40	1,67	1,68	35,72	454,09	449,98	163,60	424,00	0,42	328,55	323,76
12	Flecainide	11	582	164	1680	1669	1654	1677	1693	0,58	1676,20	1,68			449,53			418,00	0,42	322,86	
12	Flecainide	11	578	162	1720	1680	1669	1654	1677	0,58	1696,00	1,70			443,83			416,00	0,42	319,43	
12	Flecainide	11	584	164	1664	1720	1680	1669	1654	0,58	1676,30	1,68			451,06			420,00	0,42	324,39	
12	Flecainide	11	586	166	1691	1664	1720	1680	1669	0,59	1685,20	1,69			451,41			420,00	0,42	323,54	
12	Flecainide	12	580	164	1541	1532	1575	1553	1594	0,58	1549,10	1,55	1,56	38,49	466,00	461,38	161,60	416,00	0,42	334,24	331,94
12	Flecainide	12	574	160	1542	1541	1532	1575	1553	0,57	1545,20	1,55			461,76			414,00	0,41	333,05	
12	Flecainide	12	574	162	1545	1542	1541	1532	1575	0,57	1545,70	1,55			461,69			412,00	0,41	331,39	
12	Flecainide	12	576	160	1596	1545	1542	1541	1532	0,58	1568,50	1,57			459,92			416,00	0,42	332,16	
12	Flecainide	12	576	162	1606	1596	1545	1542	1541	0,58	1585,00	1,59			457,52			414,00	0,41	328,84	
12	Flecainide	13	566	162	1068	2876	1590	1068	1026	0,57	1477,60	1,48	1,32	45,56	465,63	488,25	164,40	404,00	0,40	332,36	344,18
12	Flecainide	13	538	168	1090	1068	2876	1590	1068	0,54	1312,00	1,31			469,69			370,00	0,37	323,02	
12	Flecainide	13	580	162	1342	1090	1068	2876	1590	0,58	1442,40	1,44			482,93			418,00	0,42	348,04	
12	Flecainide	13	580	164	1046	1342	1090	1068	2876	0,58	1294,80	1,29			509,71			416,00	0,42	365,59	
12	Flecainide	13	528	166	998	1046	1342	1090	1068	0,53	1058,20	1,06			513,27			362,00	0,36	351,90	
13	Baseline standing	-5	554	164	838	1032	3028	932	1098	0,55	1131,20	1,13	1,39	43,11	520,88	468,33	161,20	390,00	0,39	366,69	329,18
13	Baseline standing	-5	526	162	1015	838	1032	3028	932	0,53	1174,30	1,17			485,40			364,00	0,36	335,90	
13	Baseline standing	-5	516	160	2673	1015	838	1032	3028	0,52	2029,30	2,03			362,22			356,00	0,36	249,91	
13	Baseline standing	-5	554	164	1181	2673	1015	838	1032	0,55	1413,60	1,41			465,96			390,00	0,39	328,02	
13	Baseline standing	-5	558	156	1043	1181	2673	1015	838	0,56	1210,30	1,21			507,21			402,00	0,40	365,41	
13	Baseline standing	-4	550	162	819	1063	2166	821	852	0,55	1006,00	1,01	1,16	51,92	548,36	503,98	161,20	388,00	0,39	386,84	353,31
13	Baseline standing	-4	536	162	937	819	1063	2166	821	0,54	1037,30	1,04			526,27			374,00	0,37	367,21	
13	Baseline standing	-4	554	156	1058	937	819	1063	2166	0,55	1121,20	1,12			523,20			398,00	0,40	375,87	
13	Baseline standing	-4	520	166	1801	1058	937	819	1063	0,52	1394,00	1,39			440,42			354,00	0,35	299,83	
13	Baseline standing	-4	532	160	1157	1801	1058	937	819	0,53	1220,10	1,22			481,63			372,00	0,37	336,78	
13	Baseline standing	-3	542	154	1135	1605	1128	904	1073	0,54	1199,00	1,20	1,27	47,09	494,98	485,03	158,00	388,00	0,39	354,34	344,61
13	Baseline standing	-3	538	154	1169	1135	1605	1128	904	0,54	1175,20	1,18			496,28			384,00	0,38	354,22	
13	Baseline standing	-3	556	162	1313	1169	1135	1605	1128	0,56	1277,10	1,28			492,00			394,00	0,39	348,65	
13	Baseline standing	-3	552	162	1094	1313	1169	1135	1605	0,55	1200,50	1,20			503,80			390,00	0,39	355,95	

Table 2 continued

13	Baseline standing	-3	540	158	1878	1094	1313	1169	1135	0,54	1519,50	1,52			438,07			382,00	0,38	309,89	
13	Baseline standing	-2	546	158	1071	3053	1237	735	1187	0,55	1462,00	1,46	1,43	41,93	451,56	454,15	159,20	388,00	0,39	320,89	319,27
13	Baseline standing	-2	524	160	807	1071	3053	1237	735	0,52	1120,20	1,12			495,09			364,00	0,36	343,92	
13	Baseline standing	-2	504	160	2279	807	1071	3053	1237	0,50	1837,00	1,84			371,86			344,00	0,34	253,81	
13	Baseline standing	-2	542	162	1302	2279	807	1071	3053	0,54	1599,90	1,60			428,50			380,00	0,38	300,43	
13	Baseline standing	-2	558	156	918	1302	2279	807	1071	0,56	1135,10	1,14			523,74			402,00	0,40	377,32	
13	Baseline standing	-1	514	156	3272	1367	782	1334	3494	0,51	2470,40	2,47	1,53	39,10	327,02	441,68	157,20	358,00	0,36	227,77	311,20
13	Baseline standing	-1	554	156	868	3272	1367	782	1334	0,55	1436,70	1,44			462,20			398,00	0,40	332,05	
13	Baseline standing	-1	514	158	1070	868	3272	1367	782	0,51	1250,70	1,25			459,61			356,00	0,36	318,33	
13	Baseline standing	-1	534	162	1033	1070	868	3272	1367	0,53	1281,20	1,28			471,77			372,00	0,37	328,65	
13	Baseline standing	-1	542	154	1014	1033	1070	868	3272	0,54	1234,60	1,23			487,79			388,00	0,39	349,20	
13	Flecainide	1	554	156	994	3291	1086	858	1598	0,55	1509,40	1,51	1,42	42,31	450,93	451,03	156,00	398,00	0,40	323,95	319,38
13	Flecainide	1	542	154	986	994	3291	1086	858	0,54	1215,30	1,22			491,65			388,00	0,39	351,96	
13	Flecainide	1	508	160	1624	986	994	3291	1086	0,51	1546,30	1,55			408,52			348,00	0,35	279,85	
13	Flecainide	1	546	154	1486	1624	986	994	3291	0,55	1594,90	1,59			432,34			392,00	0,39	310,40	
13	Flecainide	1	522	156	1134	1486	1624	986	994	0,52	1224,60	1,22			471,71			366,00	0,37	330,74	
13	Flecainide	2	562	156	1150	1150	1086	1858	1612	0,56	1260,60	1,26	1,54	39,02	500,55	452,04	157,60	406,00	0,41	361,61	322,45
13	Flecainide	2	488	158	3304	1150	1150	1086	1858	0,49	2291,40	2,29			322,38			330,00	0,33	218,00	
13	Flecainide	2	592	158	1060	3304	1150	1150	1086	0,59	1529,40	1,53			478,70			434,00	0,43	350,94	
13	Flecainide	2	548	158	974	1060	3304	1150	1150	0,55	1259,40	1,26			488,31			390,00	0,39	347,52	
13	Flecainide	2	546	158	1204	974	1060	3304	1150	0,55	1348,20	1,35			470,24			388,00	0,39	334,16	
13	Flecainide	3	530	162	1056	958	626	744	814	0,53	938,00	0,94	1,11	54,24	547,24	497,82	157,60	368,00	0,37	379,97	345,45
13	Flecainide	3	522	156	714	1056	958	626	744	0,52	801,00	0,80			583,25			366,00	0,37	408,94	
13	Flecainide	3	510	158	1630	714	1056	958	626	0,51	1221,80	1,22			461,39			352,00	0,35	318,45	
13	Flecainide	3	502	158	1760	1630	714	1056	958	0,50	1478,80	1,48			412,81			344,00	0,34	282,88	
13	Flecainide	3	506	154	798	1760	1630	714	1056	0,51	1091,00	1,09			484,44			352,00	0,35	337,00	
13	Flecainide	4	518	162	792	892	1004	1214	1112	0,52	907,40	0,91	0,79	76,01	543,79	580,09	160,80	356,00	0,36	373,72	398,56
13	Flecainide	4	496	162	654	792	892	1004	1214	0,50	796,40	0,80			555,80			334,00	0,33	374,27	
13	Flecainide	4	518	158	706	654	792	892	1004	0,52	752,60	0,75			597,10			360,00	0,36	414,97	
13	Flecainide	4	526	156	836	706	654	792	892	0,53	793,00	0,79			590,68			370,00	0,37	415,49	
13	Flecainide	4	512	166	630	836	706	654	792	0,51	697,40	0,70			613,10			346,00	0,35	414,32	
13	Flecainide	5	576	160	1268	970	2248	1154	1104	0,58	1278,60	1,28	1,51	39,80	509,40	432,47	160,40	416,00	0,42	367,90	301,22
13	Flecainide	5	520	160	1574	1268	970	2248	1154	0,52	1477,80	1,48			427,76			360,00	0,36	296,14	
13	Flecainide	5	502	156	1318	1574	1268	970	2248	0,50	1422,40	1,42			420,91			346,00	0,35	290,11	
13	Flecainide	5	526	168	2460	1318	1574	1268	970	0,53	1874,80	1,87			384,16			358,00	0,36	261,46	
13	Flecainide	5	512	158	1154	2460	1318	1574	1268	0,51	1485,00	1,49			420,15			354,00	0,35	290,50	

Table 2 continued

13	Flecainide	6	494	160	942	860	1166	1168	1076	0,49	984,00	0,98	1,08	55,37	498,00	483,75	161,20	334,00	0,33	336,70	328,03
13	Flecainide	6	514	162	888	942	860	1166	1168	0,51	951,80	0,95			526,85			352,00	0,35	360,80	
13	Flecainide	6	500	158	1164	888	942	860	1166	0,50	1056,40	1,06			486,47			342,00	0,34	332,75	
13	Flecainide	6	512	162	1132	1164	888	942	860	0,51	1067,80	1,07			495,48			350,00	0,35	338,71	
13	Flecainide	6	480	164	1664	1132	1164	888	942	0,48	1357,80	1,36			411,93			316,00	0,32	271,19	
13	Flecainide	7	596	172	1272	1294	1314	1216	1352	0,60	1283,00	1,28	1,28	46,83	526,18	528,00	174,00	424,00	0,42	374,33	374,25
13	Flecainide	7	598	174	1234	1272	1294	1314	1216	0,60	1253,80	1,25			534,06			424,00	0,42	378,66	
13	Flecainide	7	602	180	1266	1234	1272	1294	1314	0,60	1267,80	1,27			534,65			422,00	0,42	374,79	
13	Flecainide	7	596	174	1308	1266	1234	1272	1294	0,60	1287,20	1,29			525,32			422,00	0,42	371,95	
13	Flecainide	7	596	170	1352	1308	1266	1234	1272	0,60	1314,80	1,31			519,78			426,00	0,43	371,52	
13	Flecainide	8	558	164	982	977	977	979	973	0,56	979,30	0,98	0,97	61,54	563,87	567,98	164,80	394,00	0,39	398,14	401,07
13	Flecainide	8	556	166	976	982	977	977	979	0,56	977,70	0,98			562,31			390,00	0,39	394,42	
13	Flecainide	8	558	168	971	976	982	977	977	0,56	974,30	0,97			565,31			390,00	0,39	395,11	
13	Flecainide	8	560	158	968	971	976	982	977	0,56	971,70	0,97			568,10			402,00	0,40	407,81	
13	Flecainide	8	572	168	970	968	971	976	982	0,57	971,50	0,97			580,33			404,00	0,40	409,88	
13	Flecainide	9	560	168	967	948	948	948	1056	0,56	968,30	0,97	0,98	61,07	569,09	570,80	164,40	392,00	0,39	398,36	404,87
13	Flecainide	9	570	168	955	967	948	948	948	0,57	955,30	0,96			583,18			402,00	0,40	411,30	
13	Flecainide	9	570	162	985	955	967	948	948	0,57	969,80	0,97			578,81			408,00	0,41	414,30	
13	Flecainide	9	570	164	1115	985	955	967	948	0,57	1041,50	1,04			558,53			406,00	0,41	397,83	
13	Flecainide	9	558	160	960	960	1115	985	955	0,56	977,50	0,98			564,39			398,00	0,40	402,55	
13	Flecainide	10	540	168	935	935	935	1104	950	0,54	953,40	0,95	1,01	59,50	553,04	562,96	163,60	372,00	0,37	380,98	399,90
13	Flecainide	10	562	162	972	935	935	935	1104	0,56	970,40	0,97			570,51			400,00	0,40	406,05	
13	Flecainide	10	582	162	1198	972	935	935	935	0,58	1073,90	1,07			561,62			420,00	0,42	405,29	
13	Flecainide	10	572	164	979	1198	972	935	935	0,57	1013,30	1,01			568,23			408,00	0,41	405,31	
13	Flecainide	10	570	162	1049	979	1198	972	935	0,57	1030,80	1,03			561,42			408,00	0,41	401,86	
13	Flecainide	11	550	168	773	773	773	773	784	0,55	774,10	0,77	0,78	76,53	625,12	603,81	166,40	382,00	0,38	434,18	415,84
13	Flecainide	11	516	166	836	773	773	773	773	0,52	804,50	0,80			575,29			350,00	0,35	390,22	
13	Flecainide	11	544	166	740	836	773	773	773	0,54	769,10	0,77			620,31			378,00	0,38	431,02	
13	Flecainide	11	546	166	770	740	836	773	773	0,55	771,20	0,77			621,74			380,00	0,38	432,71	
13	Flecainide	11	516	166	824	770	740	836	773	0,52	800,90	0,80			576,58			350,00	0,35	391,09	
13	Flecainide	12	674	164	1677	1696	1698	1707	1710	0,67	1689,20	1,69	1,69	35,44	518,58	518,91	163,20	510,00	0,51	392,40	393,48
13	Flecainide	12	678	164	1694	1677	1696	1698	1707	0,68	1692,50	1,69			521,15			514,00	0,51	395,09	
13	Flecainide	12	674	164	1706	1694	1677	1696	1698	0,67	1698,90	1,70			517,10			510,00	0,51	391,28	
13	Flecainide	12	676	158	1697	1706	1694	1677	1696	0,68	1696,40	1,70			519,02			518,00	0,52	397,71	
13	Flecainide	12	674	166	1683	1697	1706	1694	1677	0,67	1688,60	1,69			518,68			508,00	0,51	390,93	
13	Flecainide	13	650	164	967	967	967	982	966	0,65	968,40	0,97	0,98	60,97	660,52	653,46	162,40	486,00	0,49	493,87	489,68

Table 2 continued

13	Flecainide	13	668	168	972	967	967	967	982	0,67	971,00	0,97			677,90			500,00	0,50	507,41	
13	Flecainide	13	662	160	957	972	967	967	967	0,66	963,00	0,96			674,60			502,00	0,50	511,55	
13	Flecainide	13	668	160	986	957	972	967	967	0,67	975,00	0,98			676,51			508,00	0,51	514,47	
13	Flecainide	13	590	160	1112	986	957	972	967	0,59	1042,80	1,04			577,77			430,00	0,43	421,08	

Table 2 QTc, QRS, JTc, and HR measurements and calculations of the conscious study. Measurements and calculations were carried out before (baseline), during and after intravenous flecainide infusion. The QT and QRS intervals of each of the six horses (horse 8 to 13) were measured on 5 consecutive beats within each recording period (time -5 to 13). Recording periods were just before drug administration (t=-1), and at 5 (t=-2), 10 (t=-3), 15 (t=-4), and 20 (t=-5) minutes before drug administration, immediately after starting drug administration (t=1), 1 (t=2), 2 (t=3), 3 (t=4), 4 (t=5), 5 (t=6), 10 (t=7), 15 (t=8), 20 (t=9), 25 (t=10), 30 (t=11), 45 (t=12), and 60 (t=13) minutes after drug administration. The RR intervals were likewise calculated on 5 consecutive beats where RRn-1 is the RR interval just previous to a QT interval, RRn-2 the second interval, RR-3 the third interval, RR-4 the fourth interval, and RR-5 the fifth interval. The modified RR interval (RRmod) was calculated using the RRmod formula (5*RRn-1 + 2*RRn-2 + RRn-3 +RRn-4 +RRn-5)/10), and a mean was calculated. The QTc intervals were calculated using Bazett's formula for correction (QTc=QT/√RRmod), and a mean for each recording period was calculated (QTc Bazett's mean). HR was calculated as 60/RRmod (mean). JT intervals were calculated as QTn-QRSn and JTc was calculated using Bazett's formula. A JTc mean was then calculated.

Table 2 continued

Unconscious study

Horse ID	Intervention	Time	QTn	RRn-1	RRn-2	RRn-3	RRn-4	RRn-5	QTn	RRmod	RRmod	RRmod (mean)	HR	QTc (Bazetts)	QTc (Bazetts)	QTc (Bazetts) (mean)
			[msec]	[msec]	[msec]	[msec]	[msec]	[msec]	[sec]	[msec]	[sec]	[sec]	[Bpm]	[sec]	[msec]	[msec]
8	Baseline Anesthesia	-5	888	1946	1951	1952	1951	1954	0,89	1948,90	1,95	1,95	30,74	0,64	636,09	628,48
8	Baseline Anesthesia	-5	870	1957	1946	1951	1952	1951	0,87	1953,10	1,95			0,62	622,53	
8	Baseline Anesthesia	-5	870	1953	1957	1946	1951	1952	0,87	1952,80	1,95			0,62	622,57	
8	Baseline Anesthesia	-5	874	1953	1953	1957	1946	1951	0,87	1952,50	1,95			0,63	625,48	
8	Baseline Anesthesia	-5	888	1950	1953	1953	1957	1946	0,89	1951,20	1,95			0,64	635,71	
8	Baseline Anesthesia	-4	940	2635	2651	2655	2666	2661	0,94	2645,90	2,65	2,64	22,74	0,58	577,88	579,44
8	Baseline Anesthesia	-4	944	2638	2635	2651	2655	2666	0,94	2643,20	2,64			0,58	580,64	
8	Baseline Anesthesia	-4	936	2639	2638	2635	2651	2655	0,94	2641,20	2,64			0,58	575,94	
8	Baseline Anesthesia	-4	938	2629	2639	2638	2635	2651	0,94	2634,70	2,63			0,58	577,88	
8	Baseline Anesthesia	-4	948	2621	2629	2639	2638	2635	0,95	2627,50	2,63			0,58	584,84	
8	Baseline Anesthesia	-3	834	2368	2844	2398	2241	2149	0,83	2431,60	2,43	2,95	20,32	0,53	534,84	488,13
8	Baseline Anesthesia	-3	840	3725	2368	2844	2398	2241	0,84	3084,40	3,08			0,48	478,29	
8	Baseline Anesthesia	-3	838	3562	3725	2368	2844	2398	0,84	3287,00	3,29			0,46	462,22	
8	Baseline Anesthesia	-3	840	2291	3562	3725	2368	2844	0,84	2751,60	2,75			0,51	506,39	
8	Baseline Anesthesia	-3	822	3569	2291	3562	3725	2368	0,82	3208,20	3,21			0,46	458,92	
8	Baseline Anesthesia	-2	820	4700	3596	3439	1853	2549	0,82	3853,30	3,85	3,20	18,76	0,42	417,73	464,05
8	Baseline Anesthesia	-2	834	2400	4700	3596	3439	1853	0,83	3028,80	3,03			0,48	479,22	
8	Baseline Anesthesia	-2	824	2662	2400	4700	3596	3439	0,82	2984,50	2,98			0,48	476,97	
8	Baseline Anesthesia	-2	820	2307	2662	2400	4700	3596	0,82	2755,50	2,76			0,49	493,98	
8	Baseline Anesthesia	-2	830	3858	2307	2662	2400	4700	0,83	3366,60	3,37			0,45	452,36	
8	Baseline Anesthesia	-1	820	3181	2518	3402	1806	3869	0,82	3001,80	3,00	2,80	21,43	0,47	473,29	489,78
8	Baseline Anesthesia	-1	822	2993	3181	2518	3402	1806	0,82	2905,30	2,91			0,48	482,25	
8	Baseline Anesthesia	-1	832	2523	2993	3181	2518	3402	0,83	2770,20	2,77			0,50	499,88	
8	Baseline Anesthesia	-1	814	2226	2523	2993	3181	2518	0,81	2486,80	2,49			0,52	516,18	
8	Baseline Anesthesia	-1	804	3045	2226	2523	2993	3181	0,80	2837,40	2,84			0,48	477,30	
8	Flecainide	1	875	2086	2988	3140	2218	2157	0,88	2392,10	2,39	3,46	17,33	0,57	565,74	468,58
8	Flecainide	1	850	5598	2086	2988	3140	2218	0,85	4050,80	4,05			0,42	422,33	
8	Flecainide	1	840	3479	5598	2086	2988	3140	0,84	3680,50	3,68			0,44	437,85	
8	Flecainide	1	865	4481	3479	5598	2086	2988	0,87	4003,50	4,00			0,43	432,31	

Table 3

8	Flecainide	1	865	2346	4481	3479	5598	2086	0,87	3185,50	3,19			0,48	484,65	
8	Flecainide	2	852	4596	2406	2192	3298	1906	0,85	3518,80	3,52	3,40	17,63	0,45	454,19	461,35
8	Flecainide	2	865	3285	4596	2406	2192	3298	0,87	3351,30	3,35			0,47	472,51	
8	Flecainide	2	845	3978	3285	4596	2406	2192	0,85	3565,40	3,57			0,45	447,51	
8	Flecainide	2	830	3240	3978	3285	4596	2406	0,83	3444,30	3,44			0,45	447,23	
8	Flecainide	2	860	2613	3240	3978	3285	4596	0,86	3140,40	3,14			0,49	485,30	
8	Flecainide	3	885	1935	3151	3161	3926	2719	0,89	2578,30	2,58	2,96	20,30	0,55	551,16	500,54
8	Flecainide	3	840	2903	1935	3151	3161	3926	0,84	2862,30	2,86			0,50	496,50	
8	Flecainide	3	850	2037	2903	1935	3151	3161	0,85	2423,80	2,42			0,55	545,97	
8	Flecainide	3	860	4552	2037	2903	1935	3151	0,86	3482,30	3,48			0,46	460,86	
8	Flecainide	3	830	3662	4552	2037	2903	1935	0,83	3428,90	3,43			0,45	448,23	
8	Flecainide	4	855	2195	2338	2434	4685	3027	0,86	2579,70	2,58	3,34	17,98	0,53	532,33	473,04
8	Flecainide	4	830	3899	2195	2338	2434	4685	0,83	3334,20	3,33			0,45	454,55	
8	Flecainide	4	835	3879	3899	2195	2338	2434	0,84	3416,00	3,42			0,45	451,78	
8	Flecainide	4	895	3030	3879	3899	2195	2338	0,90	3134,00	3,13			0,51	505,56	
8	Flecainide	4	865	5237	3030	3879	3899	2195	0,87	4221,80	4,22			0,42	420,99	
8	Flecainide	5	855	2688	1931	2282	2121	2169	0,86	2387,40	2,39	3,04	19,73	0,55	553,35	503,67
8	Flecainide	5	870	2505	2688	1931	2282	2121	0,87	2423,50	2,42			0,56	558,85	
8	Flecainide	5	840	4193	2505	2688	1931	2282	0,84	3287,60	3,29			0,46	463,28	
8	Flecainide	5	870	2667	4193	2505	2688	1931	0,87	2884,50	2,88			0,51	512,25	
8	Flecainide	5	885	5503	2667	4193	2505	2688	0,89	4223,50	4,22			0,43	430,63	
8	Flecainide	6	885	3851	2375	2605	2710	3112	0,89	3243,20	3,24	4,10	14,62	0,49	491,42	440,84
8	Flecainide	6	900	4959	3851	2375	2605	2710	0,90	4018,70	4,02			0,45	448,95	
8	Flecainide	6	875	5300	4959	3851	2375	2605	0,88	4524,90	4,52			0,41	411,34	
8	Flecainide	6	895	4054	5300	4959	3851	2375	0,90	4205,50	4,21			0,44	436,43	
8	Flecainide	6	885	4605	4054	5300	4959	3851	0,89	4524,30	4,52			0,42	416,07	
8	Flecainide	7	920	3141	2515	2549	2564	2191	0,92	2803,90	2,80	3,23	18,58	0,55	549,42	520,61
8	Flecainide	7	935	4260	3141	2515	2549	2564	0,94	3521,00	3,52			0,50	498,29	
8	Flecainide	7	935	4302	4260	3141	2515	2549	0,94	3823,50	3,82			0,48	478,17	
8	Flecainide	7	935	2444	4302	4260	3141	2515	0,94	3074,00	3,07			0,53	533,29	
8	Flecainide	7	930	2529	2444	4302	4260	3141	0,93	2923,60	2,92			0,54	543,91	
8	Flecainide	8	970	2642	2983	3824	2223	3224	0,97	2844,70	2,84	3,34	17,99	0,58	575,11	542,95
8	Flecainide	8	955	3153	2642	2983	3824	2223	0,96	3007,90	3,01			0,55	550,64	
8	Flecainide	8	1030	4952	3153	2642	2983	3824	1,03	4051,50	4,05			0,51	511,72	
8	Flecainide	8	955	2444	4952	3153	2642	2983	0,96	3090,20	3,09			0,54	543,26	
8	Flecainide	8	1025	4241	2444	4952	3153	2642	1,03	3684,00	3,68			0,53	534,03	

Table 3 continued

9	Baseline Anesthesia	-5	866	2100	2054	2081	2103	2102	0,87	2089,40	2,09	2,10	28,64	0,60	599,11	603,55
9	Baseline Anesthesia	-5	860	2102	2100	2054	2081	2103	0,86	2094,80	2,09			0,59	594,19	
9	Baseline Anesthesia	-5	878	2101	2102	2100	2054	2081	0,88	2094,40	2,09			0,61	606,69	
9	Baseline Anesthesia	-5	890	2100	2101	2102	2100	2054	0,89	2095,80	2,10			0,61	614,77	
9	Baseline Anesthesia	-5	874	2101	2100	2101	2102	2100	0,87	2100,80	2,10			0,60	603,00	
9	Baseline Anesthesia	-4	864	2135	2129	2128	2124	2137	0,86	2132,20	2,13	2,12	28,26	0,59	591,70	599,61
9	Baseline Anesthesia	-4	870	2132	2135	2129	2128	2124	0,87	2131,10	2,13			0,60	595,96	
9	Baseline Anesthesia	-4	884	2126	2132	2135	2129	2128	0,88	2128,60	2,13			0,61	605,91	
9	Baseline Anesthesia	-4	876	2136	2126	2132	2135	2129	0,88	2132,80	2,13			0,60	599,83	
9	Baseline Anesthesia	-4	874	2046	2136	2126	2132	2135	0,87	2089,50	2,09			0,60	604,63	
9	Baseline Anesthesia	-3	754	1835	1672	1163	1108	1455	0,75	1624,50	1,62	1,50	39,91	0,59	591,58	593,88
9	Baseline Anesthesia	-3	706	1314	1835	1672	1163	1108	0,71	1418,30	1,42			0,59	592,82	
9	Baseline Anesthesia	-3	730	1318	1314	1835	1672	1163	0,73	1388,80	1,39			0,62	619,45	
9	Baseline Anesthesia	-3	742	1636	1318	1314	1835	1672	0,74	1563,70	1,56			0,59	593,37	
9	Baseline Anesthesia	-3	706	1497	1636	1318	1314	1835	0,71	1522,40	1,52			0,57	572,19	
9	Baseline Anesthesia	-2	750	1607	2455	1414	1566	1206	0,75	1713,10	1,71	1,64	36,68	0,57	573,02	560,07
9	Baseline Anesthesia	-2	714	1455	1607	2455	1414	1566	0,71	1592,40	1,59			0,57	565,81	
9	Baseline Anesthesia	-2	708	1836	1455	1607	2455	1414	0,71	1756,60	1,76			0,53	534,19	
9	Baseline Anesthesia	-2	706	1446	1836	1455	1607	2455	0,71	1641,90	1,64			0,55	550,97	
9	Baseline Anesthesia	-2	700	1392	1446	1836	1455	1607	0,70	1475,00	1,48			0,58	576,37	
9	Baseline Anesthesia	-1	756	1665	1269	2324	2563	2047	0,76	1779,70	1,78	1,76	34,13	0,57	566,69	559,79
9	Baseline Anesthesia	-1	730	2106	1665	1269	2324	2563	0,73	2001,60	2,00			0,52	515,98	
9	Baseline Anesthesia	-1	716	1375	2106	1665	1269	2324	0,72	1634,50	1,63			0,56	560,04	
9	Baseline Anesthesia	-1	756	1557	1375	2106	1665	1269	0,76	1557,50	1,56			0,61	605,77	
9	Baseline Anesthesia	-1	742	1982	1557	1375	2106	1665	0,74	1817,00	1,82			0,55	550,46	
9	Flecainide	1	740	1737	1904	1809	1834	1613	0,74	1774,90	1,77	2,31	25,96	0,56	555,45	522,08
9	Flecainide	1	788	3844	1737	1904	1809	1834	0,79	2824,10	2,82			0,47	468,91	
9	Flecainide	1	834	1983	3844	1737	1904	1809	0,83	2305,30	2,31			0,55	549,29	
9	Flecainide	1	774	2632	1983	3844	1737	1904	0,77	2461,10	2,46			0,49	493,37	
9	Flecainide	1	804	1813	2632	1983	3844	1737	0,80	2189,30	2,19			0,54	543,38	
9	Flecainide	2	694	1416	1236	1350	2187	2059	0,69	1514,80	1,51	1,51	39,83	0,56	563,87	579,16
9	Flecainide	2	700	1402	1416	1236	1350	2187	0,70	1461,50	1,46			0,58	579,03	
9	Flecainide	2	736	1679	1402	1416	1236	1350	0,74	1520,10	1,52			0,60	596,96	
9	Flecainide	2	728	1622	1679	1402	1416	1236	0,73	1552,20	1,55			0,58	584,33	
9	Flecainide	2	696	1417	1622	1679	1402	1416	0,70	1482,60	1,48			0,57	571,61	
9	Flecainide	3	740	1647	2493	1547	1634	1546	0,74	1794,80	1,79	1,81	33,15	0,55	552,36	552,19

Table 3 continued

9	Flecainide	3	752	1758	1647	2493	1547	1634	0,75	1775,80	1,78			0,56	564,31	
9	Flecainide	3	738	1527	1758	1647	2493	1547	0,74	1683,80	1,68			0,57	568,74	
9	Flecainide	3	744	2230	1527	1758	1647	2493	0,74	2010,20	2,01			0,52	524,75	
9	Flecainide	3	736	1693	2230	1527	1758	1647	0,74	1785,70	1,79			0,55	550,77	
9	Flecainide	4	744	1476	2715	1412	2087	1594	0,74	1790,30	1,79	1,75	34,22	0,56	556,05	549,90
9	Flecainide	4	706	1496	1476	2715	1412	2087	0,71	1664,60	1,66			0,55	547,20	
9	Flecainide	4	720	1909	1496	1476	2715	1412	0,72	1814,00	1,81			0,53	534,58	
9	Flecainide	4	714	2070	1909	1496	1476	2715	0,71	1985,50	1,99			0,51	506,71	
9	Flecainide	4	744	1221	2070	1909	1496	1476	0,74	1512,60	1,51			0,60	604,94	
9	Flecainide	5	744	2184	1805	2641	1670	2002	0,74	2084,30	2,08	1,73	34,63	0,52	515,34	558,99
9	Flecainide	5	776	1727	2184	1805	2641	1670	0,78	1911,90	1,91			0,56	561,21	
9	Flecainide	5	720	1202	1727	2184	1805	2641	0,72	1609,40	1,61			0,57	567,55	
9	Flecainide	5	706	1295	1202	1727	2184	1805	0,71	1459,50	1,46			0,58	584,39	
9	Flecainide	5	716	1655	1295	1202	1727	2184	0,72	1597,80	1,60			0,57	566,44	
9	Flecainide	6	812	2811	2016	1928	2769	2228	0,81	2501,20	2,50	2,04	29,41	0,51	513,43	543,48
9	Flecainide	6	776	1537	2811	2016	1928	2769	0,78	2002,00	2,00			0,55	548,44	
9	Flecainide	6	752	1441	1537	2811	2016	1928	0,75	1703,40	1,70			0,58	576,18	
9	Flecainide	6	720	1745	1441	1537	2811	2016	0,72	1797,10	1,80			0,54	537,09	
9	Flecainide	6	804	2541	1745	1441	1537	2811	0,80	2198,40	2,20			0,54	542,25	
9	Flecainide	7	746	1463	1585	1758	1188	1766	0,75	1519,70	1,52	1,75	34,22	0,61	605,15	586,39
9	Flecainide	7	780	2537	1463	1585	1758	1188	0,78	2014,20	2,01			0,55	549,60	
9	Flecainide	7	778	1691	2537	1463	1585	1758	0,78	1833,50	1,83			0,57	574,56	
9	Flecainide	7	788	1591	1691	2537	1463	1585	0,79	1692,20	1,69			0,61	605,76	
9	Flecainide	7	780	1641	1591	1691	2537	1463	0,78	1707,80	1,71			0,60	596,86	
9	Flecainide	8	804	1325	2322	2930	1364	1597	0,80	1716,00	1,72	1,99	30,09	0,61	613,76	588,48
9	Flecainide	8	812	2651	1325	2322	2930	1364	0,81	2252,10	2,25			0,54	541,08	
9	Flecainide	8	828	2754	2651	1325	2322	2930	0,83	2564,90	2,56			0,52	517,01	
9	Flecainide	8	822	1326	2754	2651	1325	2322	0,82	1843,60	1,84			0,61	605,39	
9	Flecainide	8	840	1313	1326	2754	2651	1325	0,84	1594,70	1,59			0,67	665,18	
9	Flecainide	9	832	1902	3493	2480	1854	1922	0,83	2275,20	2,28	2,38	25,25	0,55	551,59	533,65
9	Flecainide	9	812	2960	1902	3493	2480	1854	0,81	2643,10	2,64			0,50	499,46	
9	Flecainide	9	840	2028	2960	1902	3493	2480	0,84	2393,50	2,39			0,54	542,95	
9	Flecainide	9	808	1574	2028	2960	1902	3493	0,81	2028,10	2,03			0,57	567,37	
9	Flecainide	9	808	3074	1574	2028	2960	1902	0,81	2540,80	2,54			0,51	506,90	
9	Flecainide	10	786	1842	1387	2786	1461	1937	0,79	1816,80	1,82	1,73	34,77	0,58	583,13	599,92
9	Flecainide	10	780	1528	1842	1387	2786	1461	0,78	1695,80	1,70			0,60	598,97	

Table 3 continued

9	Flecainide	10	770	1359	1528	1842	1387	2786	0,77	1586,60	1,59			0,61	611,30	
9	Flecainide	10	802	2025	1359	1528	1842	1387	0,80	1760,00	1,76			0,60	604,53	
9	Flecainide	10	800	1780	2025	1359	1528	1842	0,80	1767,90	1,77			0,60	601,67	
9	Flecainide	11	818	1918	1593	1758	2799	1836	0,82	1916,90	1,92	1,96	30,66	0,59	590,82	575,40
9	Flecainide	11	780	1930	1918	1593	1758	2799	0,78	1963,60	1,96			0,56	556,63	
9	Flecainide	11	802	2394	1930	1918	1593	1758	0,80	2109,90	2,11			0,55	552,13	
9	Flecainide	11	808	1732	2394	1930	1918	1593	0,81	1888,90	1,89			0,59	587,90	
9	Flecainide	11	814	1872	1732	2394	1930	1918	0,81	1906,60	1,91			0,59	589,51	
9	Flecainide	12	764	1458	1205	1801	1457	1331	0,76	1428,90	1,43	1,57	38,23	0,64	639,13	606,46
9	Flecainide	12	760	1954	1458	1205	1801	1457	0,76	1714,90	1,71			0,58	580,36	
9	Flecainide	12	756	1336	1954	1458	1205	1801	0,76	1505,20	1,51			0,62	616,20	
9	Flecainide	12	750	1579	1336	1954	1458	1205	0,75	1518,40	1,52			0,61	608,65	
9	Flecainide	12	762	1778	1579	1336	1954	1458	0,76	1679,60	1,68			0,59	587,97	
9	Flecainide	13	794	2154	1636	1213	1900	1435	0,79	1859,00	1,86	1,92	31,24	0,58	582,35	566,21
9	Flecainide	13	772	1800	2154	1636	1213	1900	0,77	1805,70	1,81			0,57	574,51	
9	Flecainide	13	766	2290	1800	2154	1636	1213	0,77	2005,30	2,01			0,54	540,93	
9	Flecainide	13	784	1677	2290	1800	2154	1636	0,78	1855,50	1,86			0,58	575,55	
9	Flecainide	13	804	2237	1677	2290	1800	2154	0,80	2078,30	2,08			0,56	557,70	
10	Baseline Anesthesia	-5	710	1965	1346	1906	1487	1583	0,71	1749,30	1,75	1,55	38,73	0,54	536,82	556,58
10	Baseline Anesthesia	-5	706	1733	1965	1346	1906	1487	0,71	1733,40	1,73			0,54	536,24	
10	Baseline Anesthesia	-5	702	1292	1733	1965	1346	1906	0,70	1514,30	1,51			0,57	570,47	
10	Baseline Anesthesia	-5	686	1229	1292	1733	1965	1346	0,69	1377,30	1,38			0,58	584,53	
10	Baseline Anesthesia	-5	650	1255	1229	1292	1733	1965	0,65	1372,30	1,37			0,55	554,87	
10	Baseline Anesthesia	-4	666	1272	1862	1357	1242	1032	0,67	1371,50	1,37	1,43	41,85	0,57	568,69	554,94
10	Baseline Anesthesia	-4	648	1117	1272	1862	1357	1242	0,65	1259,00	1,26			0,58	577,51	
10	Baseline Anesthesia	-4	666	1839	1117	1272	1862	1357	0,67	1592,00	1,59			0,53	527,84	
10	Baseline Anesthesia	-4	674	1382	1839	1117	1272	1862	0,67	1483,90	1,48			0,55	553,30	
10	Baseline Anesthesia	-4	662	1527	1382	1839	1117	1272	0,66	1462,70	1,46			0,55	547,37	
10	Baseline Anesthesia	-3	616	1903	1359	1412	1033	1303	0,62	1598,10	1,60	1,63	36,78	0,49	487,28	497,73
10	Baseline Anesthesia	-3	638	1432	1903	1359	1412	1033	0,64	1477,00	1,48			0,52	524,97	
10	Baseline Anesthesia	-3	612	2206	1432	1903	1359	1412	0,61	1856,80	1,86			0,45	449,13	
10	Baseline Anesthesia	-3	668	1366	2206	1432	1903	1359	0,67	1593,60	1,59			0,53	529,16	
10	Baseline Anesthesia	-3	636	1606	1366	2206	1432	1903	0,64	1630,30	1,63			0,50	498,11	
10	Baseline Anesthesia	-2	596	1375	1237	1207	1021	1064	0,60	1264,10	1,26	1,30	46,11	0,53	530,10	530,08
10	Baseline Anesthesia	-2	582	1353	1375	1237	1207	1021	0,58	1298,00	1,30			0,51	510,84	
10	Baseline Anesthesia	-2	614	1469	1353	1375	1237	1207	0,61	1387,00	1,39			0,52	521,35	

Table 3 continued

10	Baseline Anesthesia	-2	610	1076	1469	1353	1375	1237	0,61	1228,30	1,23			0,55	550,40	
10	Baseline Anesthesia	-2	620	1389	1076	1469	1353	1375	0,62	1329,40	1,33			0,54	537,73	
10	Baseline Anesthesia	-1	680	1471	1486	1308	1533	1738	0,68	1490,60	1,49	1,55	38,82	0,56	556,97	544,13
10	Baseline Anesthesia	-1	656	1853	1471	1486	1308	1533	0,66	1653,40	1,65			0,51	510,17	
10	Baseline Anesthesia	-1	672	1478	1853	1471	1486	1308	0,67	1536,10	1,54			0,54	542,20	
10	Baseline Anesthesia	-1	686	1488	1478	1853	1471	1486	0,69	1520,60	1,52			0,56	556,31	
10	Baseline Anesthesia	-1	686	1500	1488	1478	1853	1471	0,69	1527,80	1,53			0,55	555,00	
10	NS8593	1	602	1123	972	2190	2422	1324	0,60	1349,50	1,35	1,30	46,32	0,52	518,22	538,29
10	NS8593	1	604	1155	1123	972	2190	2422	0,60	1360,50	1,36			0,52	517,83	
10	NS8593	1	620	1228	1155	1123	972	2190	0,62	1273,50	1,27			0,55	549,40	
10	NS8593	1	610	967	1228	1155	1123	972	0,61	1054,10	1,05			0,59	594,14	
10	NS8593	1	614	1790	967	1228	1155	1123	0,61	1439,00	1,44			0,51	511,84	
10	NS8593	2	632	1012	1798	2702	2158	1351	0,63	1486,70	1,49	2,13	28,10	0,52	518,33	449,37
10	NS8593	2	636	2663	1012	1798	2702	2158	0,64	2199,70	2,20			0,43	428,82	
10	NS8593	2	652	2775	2663	1012	1798	2702	0,65	2471,30	2,47			0,41	414,75	
10	NS8593	2	664	2589	2775	2663	1012	1798	0,66	2396,80	2,40			0,43	428,90	
10	NS8593	2	664	1914	2589	2775	2663	1012	0,66	2119,80	2,12			0,46	456,06	
10	NS8593	3	672	1872	2478	1337	2287	2531	0,67	2047,10	2,05	1,68	35,73	0,47	469,68	505,40
10	NS8593	3	634	1057	1872	2478	1337	2287	0,63	1513,10	1,51			0,52	515,41	
10	NS8593	3	642	1304	1057	1872	2478	1337	0,64	1432,10	1,43			0,54	536,47	
10	NS8593	3	634	1425	1304	1057	1872	2478	0,63	1514,00	1,51			0,52	515,26	
10	NS8593	3	674	2365	1425	1304	1057	1872	0,67	1890,80	1,89			0,49	490,16	
10	NS8593	4	664	2650	1329	1469	1311	1287	0,66	1997,50	2,00	1,95	30,79	0,47	469,81	478,13
10	NS8593	4	654	2310	2650	1329	1469	1311	0,65	2095,90	2,10			0,45	451,74	
10	NS8593	4	656	1321	2310	2650	1329	1469	0,66	1667,30	1,67			0,51	508,04	
10	NS8593	4	678	1925	1321	2310	2650	1329	0,68	1855,60	1,86			0,50	497,72	
10	NS8593	4	676	2231	1925	1321	2310	2650	0,68	2128,60	2,13			0,46	463,34	
10	NS8593	5	624	1141	1561	1180	2279	1603	0,62	1388,90	1,39	1,46	41,00	0,53	529,48	526,80
10	NS8593	5	628	1497	1141	1561	1180	2279	0,63	1478,70	1,48			0,52	516,44	
10	NS8593	5	656	2256	1497	1141	1561	1180	0,66	1815,60	1,82			0,49	486,85	
10	NS8593	5	638	1076	2256	1497	1141	1561	0,64	1409,10	1,41			0,54	537,46	
10	NS8593	5	624	1041	1076	2256	1497	1141	0,62	1225,10	1,23			0,56	563,77	
10	NS8593	6	638	1311	2044	1754	2315	1087	0,64	1579,90	1,58	1,65	36,34	0,51	507,58	490,18
10	NS8593	6	632	1520	1311	2044	1754	2315	0,63	1633,50	1,63			0,49	494,49	
10	NS8593	6	616	1486	1520	1311	2044	1754	0,62	1557,90	1,56			0,49	493,53	
10	NS8593	6	610	1069	1486	1520	1311	2044	0,61	1319,20	1,32			0,53	531,10	

Table 3 continued

10	NS8593	6	624	3037	1069	1486	1520	1311	0,62	2164,00	2,16			0,42	424,19	
10	NS8593	7	548	960	1267	1186	1534	788	0,55	1084,20	1,08	1,17	51,19	0,53	526,29	515,96
10	NS8593	7	570	1480	960	1267	1186	1534	0,57	1330,70	1,33			0,49	494,12	
10	NS8593	7	562	906	1480	960	1267	1186	0,56	1090,30	1,09			0,54	538,22	
10	NS8593	7	548	1293	906	1480	960	1267	0,55	1198,40	1,20			0,50	500,59	
10	NS8593	7	560	1128	1293	906	1480	960	0,56	1157,20	1,16			0,52	520,58	
10	NS8593	8	648	976	975	976	977	977	0,65	976,00	0,98	0,98	61,48	0,66	655,92	645,81
10	NS8593	8	642	976	976	975	976	977	0,64	976,00	0,98			0,65	649,85	
10	NS8593	8	632	976	976	976	975	976	0,63	975,90	0,98			0,64	639,76	
10	NS8593	8	630	976	976	976	976	975	0,63	975,90	0,98			0,64	637,73	
10	NS8593	8	638	976	976	976	976	976	0,64	976,00	0,98			0,65	645,80	
10	NS8593	9	598	989	967	930	941	1029	0,60	977,90	0,98	0,98	61,30	0,60	604,72	570,98
10	NS8593	9	556	1028	989	967	930	941	0,56	995,60	1,00			0,56	557,23	
10	NS8593	9	515	1026	1028	989	967	930	0,52	1007,20	1,01			0,51	513,16	
10	NS8593	9	570	908	1026	1028	989	967	0,57	957,60	0,96			0,58	582,48	
10	NS8593	9	584	940	908	1026	1028	989	0,58	955,90	0,96			0,60	597,32	
10	NS8593	10	628	692	975	977	976	976	0,63	833,90	0,83	0,92	65,35	0,69	687,71	663,79
10	NS8593	10	632	976	692	975	977	976	0,63	919,20	0,92			0,66	659,19	
10	NS8593	10	636	974	976	692	975	977	0,64	946,60	0,95			0,65	653,69	
10	NS8593	10	642	972	974	976	692	975	0,64	945,10	0,95			0,66	660,38	
10	NS8593	10	640	975	972	974	976	692	0,64	946,10	0,95			0,66	657,98	
10	NS8593	11	620	977	976	975	977	975	0,62	976,40	0,98	0,98	61,46	0,63	627,45	627,47
10	NS8593	11	624	976	977	976	975	977	0,62	976,20	0,98			0,63	631,56	
10	NS8593	11	620	976	977	976	975	977	0,62	976,20	0,98			0,63	627,51	
10	NS8593	11	620	977	976	977	976	975	0,62	976,50	0,98			0,63	627,42	
10	NS8593	11	616	976	977	976	977	976	0,62	976,30	0,98			0,62	623,43	
10	NS8593	12	562	993	1473	1006	1562	1581	0,56	1206,00	1,21	1,30	46,02	0,51	511,76	496,66
10	NS8593	12	564	1090	993	1473	1006	1562	0,56	1147,70	1,15			0,53	526,46	
10	NS8593	12	564	1608	1090	993	1473	1006	0,56	1369,20	1,37			0,48	482,00	
10	NS8593	12	574	1576	1608	1090	993	1473	0,57	1465,20	1,47			0,47	474,20	
10	NS8593	12	564	1293	1576	1608	1090	993	0,56	1330,80	1,33			0,49	488,90	
10	NS8593	13	830	2231	2242	2236	2242	2247	0,83	2236,40	2,24	2,23	26,85	0,56	555,01	552,87
10	NS8593	13	824	2229	2231	2242	2236	2242	0,82	2232,70	2,23			0,55	551,46	
10	NS8593	13	826	2235	2229	2231	2242	2236	0,83	2234,20	2,23			0,55	552,61	
10	NS8593	13	824	2236	2235	2229	2231	2242	0,82	2235,20	2,24			0,55	551,15	
10	NS8593	13	828	2232	2236	2235	2229	2231	0,83	2232,70	2,23			0,55	554,13	

Table 3 continued

11	Baseline Anesthesia	-5	646	1306	1413	1365	1874	1268	0,65	1386,30	1,39	1,45	41,43	0,55	548,66	543,50
11	Baseline Anesthesia	-5	648	1851	1306	1413	1365	1874	0,65	1651,90	1,65			0,50	504,18	
11	Baseline Anesthesia	-5	648	1208	1851	1306	1413	1365	0,65	1382,60	1,38			0,55	551,10	
11	Baseline Anesthesia	-5	666	1365	1208	1851	1306	1413	0,67	1381,10	1,38			0,57	566,71	
11	Baseline Anesthesia	-5	656	1459	1365	1208	1851	1306	0,66	1439,00	1,44			0,55	546,86	
11	Baseline Anesthesia	-4	642	1256	1794	1611	2246	1495	0,64	1522,00	1,52	1,67	35,97	0,52	520,39	507,86
11	Baseline Anesthesia	-4	634	1912	1256	1794	1611	2246	0,63	1772,30	1,77			0,48	476,23	
11	Baseline Anesthesia	-4	678	1658	1912	1256	1794	1611	0,68	1677,50	1,68			0,52	523,48	
11	Baseline Anesthesia	-4	658	1560	1658	1912	1256	1794	0,66	1607,80	1,61			0,52	518,93	
11	Baseline Anesthesia	-4	664	1934	1560	1658	1912	1256	0,66	1761,60	1,76			0,50	500,28	
11	Baseline Anesthesia	-3	662	1272	1650	1507	1498	2228	0,66	1489,30	1,49	1,51	39,64	0,54	542,46	540,01
11	Baseline Anesthesia	-3	656	1473	1272	1650	1507	1498	0,66	1456,40	1,46			0,54	543,58	
11	Baseline Anesthesia	-3	656	1578	1473	1272	1650	1507	0,66	1526,50	1,53			0,53	530,95	
11	Baseline Anesthesia	-3	666	1723	1578	1473	1272	1650	0,67	1616,60	1,62			0,52	523,81	
11	Baseline Anesthesia	-3	680	1403	1723	1578	1473	1272	0,68	1478,40	1,48			0,56	559,26	
11	Baseline Anesthesia	-2	666	1516	1603	1418	1458	1547	0,67	1520,90	1,52	1,77	33,84	0,54	540,04	506,34
11	Baseline Anesthesia	-2	678	1674	1516	1603	1418	1458	0,68	1588,10	1,59			0,54	538,01	
11	Baseline Anesthesia	-2	666	2153	1674	1516	1603	1418	0,67	1865,00	1,87			0,49	487,68	
11	Baseline Anesthesia	-2	666	1647	2153	1674	1516	1603	0,67	1733,40	1,73			0,51	505,85	
11	Baseline Anesthesia	-2	676	2590	1647	2153	1674	1516	0,68	2158,70	2,16			0,46	460,10	
11	Baseline Anesthesia	-1	684	1921	1209	1960	1861	1166	0,68	1701,00	1,70	1,62	37,09	0,52	524,45	531,10
11	Baseline Anesthesia	-1	684	1748	1921	1209	1960	1861	0,68	1761,20	1,76			0,52	515,41	
11	Baseline Anesthesia	-1	670	1636	1748	1921	1209	1960	0,67	1676,60	1,68			0,52	517,44	
11	Baseline Anesthesia	-1	690	1358	1636	1748	1921	1209	0,69	1494,00	1,49			0,56	564,51	
11	Baseline Anesthesia	-1	644	1308	1358	1636	1748	1921	0,64	1456,10	1,46			0,53	533,69	
11	NS8593	1	634	1839	2211	2153	1456	1320	0,63	1854,60	1,85	1,67	35,89	0,47	465,55	485,09
11	NS8593	1	622	1508	1839	2211	2153	1456	0,62	1703,80	1,70			0,48	476,52	
11	NS8593	1	626	1373	1508	1839	2211	2153	0,63	1608,40	1,61			0,49	493,60	
11	NS8593	1	630	1640	1373	1508	1839	2211	0,63	1650,40	1,65			0,49	490,39	
11	NS8593	1	620	1483	1640	1373	1508	1839	0,62	1541,50	1,54			0,50	499,37	
11	NS8593	2	632	2618	1393	1758	1655	2156	0,63	2144,50	2,14	1,89	31,82	0,43	431,57	463,82
11	NS8593	2	634	2030	2618	1393	1758	1655	0,63	2019,20	2,02			0,45	446,17	
11	NS8593	2	632	1885	2030	2618	1393	1758	0,63	1925,40	1,93			0,46	455,47	
11	NS8593	2	640	1431	1885	2030	2618	1393	0,64	1696,60	1,70			0,49	491,35	
11	NS8593	2	634	1408	1431	1885	2030	2618	0,63	1643,50	1,64			0,49	494,54	
11	NS8593	3	608	1252	1915	1556	2504	1527	0,61	1567,70	1,57	1,48	40,42	0,49	485,59	504,02

Table 3 continued

11	NS8593	3	624	1366	1252	1915	1556	2504	0,62	1530,90	1,53			0,50	504,33	
11	NS8593	3	610	1276	1366	1252	1915	1556	0,61	1383,50	1,38			0,52	518,61	
11	NS8593	3	614	1317	1276	1366	1252	1915	0,61	1367,00	1,37			0,53	525,15	
11	NS8593	3	610	1840	1317	1276	1366	1252	0,61	1572,80	1,57			0,49	486,40	
11	NS8593	4	612	1793	2058	1776	2433	2028	0,61	1931,80	1,93	1,77	33,89	0,44	440,32	464,52
11	NS8593	4	622	1492	1793	2058	1776	2433	0,62	1731,30	1,73			0,47	472,72	
11	NS8593	4	616	2189	1492	1793	2058	1776	0,62	1955,60	1,96			0,44	440,49	
11	NS8593	4	614	1600	2189	1492	1793	2058	0,61	1772,10	1,77			0,46	461,24	
11	NS8593	4	614	1189	1600	2189	1492	1793	0,61	1461,90	1,46			0,51	507,82	
11	NS8593	5	614	2100	1505	1860	1955	1460	0,61	1878,50	1,88	1,84	32,63	0,45	447,98	449,84
11	NS8593	5	610	1440	2100	1505	1860	1955	0,61	1672,00	1,67			0,47	471,75	
11	NS8593	5	606	1758	1440	2100	1505	1860	0,61	1713,50	1,71			0,46	462,95	
11	NS8593	5	606	2091	1758	1440	2100	1505	0,61	1901,60	1,90			0,44	439,45	
11	NS8593	5	608	2158	2091	1758	1440	2100	0,61	2027,00	2,03			0,43	427,05	
11	NS8593	6	592	1572	1430	1329	1559	1933	0,59	1554,10	1,55	1,64	36,48	0,47	474,88	466,61
11	NS8593	6	600	1378	1572	1430	1329	1559	0,60	1435,20	1,44			0,50	500,84	
11	NS8593	6	590	1534	1378	1572	1430	1329	0,59	1475,70	1,48			0,49	485,68	
11	NS8593	6	598	2456	1534	1378	1572	1430	0,60	1972,80	1,97			0,43	425,75	
11	NS8593	6	596	1694	2456	1534	1378	1572	0,60	1786,60	1,79			0,45	445,89	
11	NS8593	7	556	1181	1122	1113	1285	1690	0,56	1223,70	1,22	1,41	42,66	0,50	502,62	463,77
11	NS8593	7	542	2017	1181	1122	1113	1285	0,54	1596,70	1,60			0,43	428,93	
11	NS8593	7	538	1194	2017	1181	1122	1113	0,54	1342,00	1,34			0,46	464,41	
11	NS8593	7	548	1681	1194	2017	1181	1122	0,55	1511,30	1,51			0,45	445,76	
11	NS8593	7	556	1165	1681	1194	2017	1181	0,56	1357,90	1,36			0,48	477,13	
11	NS8593	8	544	976	976	976	976	975	0,54	975,90	0,98	0,97	61,55	0,55	550,68	548,16
11	NS8593	8	540	977	976	976	976	976	0,54	976,50	0,98			0,55	546,46	
11	NS8593	8	540	976	977	976	976	976	0,54	976,20	0,98			0,55	546,54	
11	NS8593	8	542	971	976	977	976	976	0,54	973,60	0,97			0,55	549,30	
11	NS8593	8	540	969	971	976	977	976	0,54	971,60	0,97			0,55	547,84	
11	NS8593	9	520	965	967	974	977	976	0,52	968,60	0,97	0,98	61,45	0,53	528,36	523,03
11	NS8593	9	516	992	965	967	974	977	0,52	980,80	0,98			0,52	521,03	
11	NS8593	9	512	983	992	965	967	974	0,51	980,50	0,98			0,52	517,07	
11	NS8593	9	516	974	983	992	965	967	0,52	976,00	0,98			0,52	522,31	
11	NS8593	9	520	974	974	983	992	965	0,52	975,80	0,98			0,53	526,41	
11	NS8593	10	544	964	969	973	976	976	0,54	968,30	0,97	0,98	61,46	0,55	552,83	535,60
11	NS8593	10	528	988	964	969	973	976	0,53	978,60	0,98			0,53	533,74	

Table 3 continued

11	NS8593	10	518	985	988	964	969	973	0,52	980,70	0,98			0,52	523,07	
11	NS8593	10	534	976	985	988	964	969	0,53	977,10	0,98			0,54	540,22	
11	NS8593	10	522	976	976	985	988	964	0,52	976,90	0,98			0,53	528,14	
11	NS8593	11	590	974	974	973	975	978	0,59	974,40	0,97	0,97	61,63	0,60	597,70	597,15
11	NS8593	11	584	976	974	974	973	975	0,58	975,00	0,98			0,59	591,44	
11	NS8593	11	584	976	976	974	974	973	0,58	975,30	0,98			0,59	591,35	
11	NS8593	11	590	972	976	976	974	974	0,59	973,60	0,97			0,60	597,95	
11	NS8593	11	598	965	972	976	976	974	0,60	969,50	0,97			0,61	607,33	
11	NS8593	12	532	976	975	977	977	977	0,53	976,10	0,98	0,98	61,49	0,54	538,47	539,80
11	NS8593	12	532	975	976	975	977	977	0,53	975,60	0,98			0,54	538,61	
11	NS8593	12	534	976	975	976	975	977	0,53	975,80	0,98			0,54	540,58	
11	NS8593	12	534	975	976	975	976	975	0,53	975,30	0,98			0,54	540,72	
11	NS8593	12	534	976	975	976	975	976	0,53	975,70	0,98			0,54	540,61	
11	NS8593	13	924	2230	2256	2244	2324	2407	0,92	2263,70	2,26	2,21	27,14	0,61	614,13	620,97
11	NS8593	13	920	2190	2230	2256	2244	2324	0,92	2223,40	2,22			0,62	616,99	
11	NS8593	13	926	2213	2190	2230	2256	2244	0,93	2217,50	2,22			0,62	621,84	
11	NS8593	13	922	2163	2213	2190	2230	2256	0,92	2191,70	2,19			0,62	622,79	
11	NS8593	13	924	2123	2163	2213	2190	2230	0,92	2157,40	2,16			0,63	629,08	
12	Baseline anaesthesia	-5	694	1365	1139	1032	1416	1272	0,69	1282,30	1,28	1,27	47,24	0,61	612,86	634,99
12	Baseline anaesthesia	-5	706	1293	1365	1139	1032	1416	0,71	1278,20	1,28			0,62	624,46	
12	Baseline anaesthesia	-5	736	1165	1293	1365	1139	1032	0,74	1194,70	1,19			0,67	673,36	
12	Baseline anaesthesia	-5	700	1502	1165	1293	1365	1139	0,70	1363,70	1,36			0,60	599,43	
12	Baseline anaesthesia	-5	738	1099	1502	1165	1293	1365	0,74	1232,20	1,23			0,66	664,84	
12	Baseline anaesthesia	-4	726	1242	1386	1262	1156	1235	0,73	1263,50	1,26	1,19	50,60	0,65	645,88	668,51
12	Baseline anaesthesia	-4	732	1032	1242	1386	1262	1156	0,73	1144,80	1,14			0,68	684,14	
12	Baseline anaesthesia	-4	714	905	1032	1242	1386	1262	0,71	1047,90	1,05			0,70	697,49	
12	Baseline anaesthesia	-4	734	1425	905	1032	1242	1386	0,73	1259,50	1,26			0,65	654,03	
12	Baseline anaesthesia	-4	728	1220	1425	905	1032	1242	0,73	1212,90	1,21			0,66	661,03	
12	Baseline anaesthesia	-3	842	1535	1534	1546	1544	1539	0,84	1537,20	1,54	1,54	39,02	0,68	679,12	677,74
12	Baseline anaesthesia	-3	840	1558	1535	1534	1546	1544	0,84	1548,40	1,55			0,68	675,05	
12	Baseline anaesthesia	-3	842	1531	1558	1535	1534	1546	0,84	1538,60	1,54			0,68	678,81	
12	Baseline anaesthesia	-3	840	1531	1531	1558	1535	1534	0,84	1534,40	1,53			0,68	678,13	
12	Baseline anaesthesia	-3	838	1522	1531	1531	1558	1535	0,84	1529,60	1,53			0,68	677,57	
12	Baseline anaesthesia	-2	764	1178	1177	1100	1123	906	0,76	1137,30	1,14	1,15	52,15	0,72	716,40	709,26
12	Baseline anaesthesia	-2	762	1044	1178	1177	1100	1123	0,76	1097,60	1,10			0,73	727,33	
12	Baseline anaesthesia	-2	756	1304	1044	1178	1177	1100	0,76	1206,30	1,21			0,69	688,33	

Table 3 continued

12	Baseline anaesthesia	-2	764	1272	1304	1044	1178	1177	0,76	1236,70	1,24			0,69	687,01	
12	Baseline anaesthesia	-2	754	936	1272	1304	1044	1178	0,75	1075,00	1,08			0,73	727,22	
12	Baseline anaesthesia	-1	844	1394	1402	1409	1401	1411	0,84	1399,50	1,40	1,41	42,45	0,71	713,44	711,58
12	Baseline anaesthesia	-1	842	1412	1394	1402	1409	1401	0,84	1406,00	1,41			0,71	710,10	
12	Baseline anaesthesia	-1	848	1420	1412	1394	1402	1409	0,85	1412,90	1,41			0,71	713,41	
12	Baseline anaesthesia	-1	848	1427	1420	1412	1394	1402	0,85	1418,30	1,42			0,71	712,05	
12	Baseline anaesthesia	-1	848	1446	1427	1420	1412	1394	0,85	1431,00	1,43			0,71	708,89	
12	NS8593	1	832	1552	1530	1526	1511	1506	0,83	1536,30	1,54	1,54	39,05	0,67	671,25	672,18
12	NS8593	1	832	1528	1552	1530	1526	1511	0,83	1531,10	1,53			0,67	672,39	
12	NS8593	1	832	1519	1528	1552	1530	1526	0,83	1525,90	1,53			0,67	673,54	
12	NS8593	1	834	1563	1519	1528	1552	1530	0,83	1546,30	1,55			0,67	670,69	
12	NS8593	1	836	1541	1563	1519	1528	1552	0,84	1543,00	1,54			0,67	673,01	
12	NS8593	2	844	1576	1576	1571	1576	1564	0,84	1574,30	1,57	1,57	38,14	0,67	672,66	671,65
12	NS8593	2	840	1578	1576	1576	1571	1576	0,84	1576,50	1,58			0,67	669,01	
12	NS8593	2	846	1585	1578	1576	1576	1571	0,85	1580,40	1,58			0,67	672,96	
12	NS8593	2	840	1547	1585	1578	1576	1576	0,84	1563,50	1,56			0,67	671,79	
12	NS8593	2	842	1575	1547	1585	1578	1576	0,84	1570,80	1,57			0,67	671,82	
12	NS8593	3	836	1585	1588	1560	1584	1589	0,84	1583,40	1,58	1,58	37,95	0,66	664,37	663,28
12	NS8593	3	834	1570	1585	1588	1560	1584	0,83	1575,20	1,58			0,66	664,50	
12	NS8593	3	836	1603	1570	1585	1588	1560	0,84	1588,80	1,59			0,66	663,24	
12	NS8593	3	834	1565	1603	1570	1585	1588	0,83	1577,40	1,58			0,66	664,04	
12	NS8593	3	830	1583	1565	1603	1570	1585	0,83	1580,30	1,58			0,66	660,25	
12	NS8593	4	838	1557	1547	1543	1538	1541	0,84	1550,10	1,55	1,56	38,53	0,67	673,08	668,37
12	NS8593	4	832	1559	1557	1547	1543	1538	0,83	1553,70	1,55			0,67	667,48	
12	NS8593	4	836	1578	1559	1557	1547	1543	0,84	1565,50	1,57			0,67	668,16	
12	NS8593	4	834	1546	1578	1559	1557	1547	0,83	1554,90	1,55			0,67	668,83	
12	NS8593	4	830	1565	1546	1578	1559	1557	0,83	1561,10	1,56			0,66	664,30	
12	NS8593	5	826	1519	1525	1559	1574	1582	0,83	1536,00	1,54	1,53	39,09	0,67	666,48	662,18
12	NS8593	5	818	1524	1519	1525	1559	1574	0,82	1531,60	1,53			0,66	660,97	
12	NS8593	5	820	1536	1524	1519	1525	1559	0,82	1533,10	1,53			0,66	662,26	
12	NS8593	5	818	1541	1536	1524	1519	1525	0,82	1534,50	1,53			0,66	660,34	
12	NS8593	5	820	1547	1541	1536	1524	1519	0,82	1539,60	1,54			0,66	660,86	
12	NS8593	6	818	1558	1542	1527	1516	1504	0,82	1542,10	1,54	1,56	38,57	0,66	658,71	656,83
12	NS8593	6	820	1591	1558	1542	1527	1516	0,82	1565,60	1,57			0,66	655,35	
12	NS8593	6	822	1565	1591	1558	1542	1527	0,82	1563,40	1,56			0,66	657,41	
12	NS8593	6	818	1571	1565	1591	1558	1542	0,82	1567,60	1,57			0,65	653,33	

Table 3 continued

12	NS8593	6	818	1507	1571	1565	1591	1558	0,82	1539,10	1,54			0,66	659,36	
12	NS8593	7	780	1307	1297	1292	1282	1273	0,78	1297,60	1,30	1,31	45,70	0,68	684,74	680,43
12	NS8593	7	780	1303	1307	1297	1292	1282	0,78	1300,00	1,30			0,68	684,11	
12	NS8593	7	778	1319	1303	1307	1297	1292	0,78	1309,70	1,31			0,68	679,82	
12	NS8593	7	776	1337	1319	1303	1307	1297	0,78	1323,00	1,32			0,67	674,66	
12	NS8593	7	784	1347	1337	1319	1303	1307	0,78	1333,80	1,33			0,68	678,85	
12	NS8593	8	778	1098	1147	1067	1083	1048	0,78	1098,20	1,10	1,14	52,55	0,74	742,40	735,03
12	NS8593	8	792	1145	1098	1147	1067	1083	0,79	1121,80	1,12			0,75	747,77	
12	NS8593	8	782	1170	1145	1098	1147	1067	0,78	1145,20	1,15			0,73	730,75	
12	NS8593	8	786	1172	1170	1145	1098	1147	0,79	1159,00	1,16			0,73	730,10	
12	NS8593	8	788	1217	1172	1170	1145	1098	0,79	1184,20	1,18			0,72	724,13	
12	NS8593	9	724	976	977	976	975	975	0,72	976,00	0,98	0,97	61,56	0,73	732,85	743,09
12	NS8593	9	732	975	976	977	976	975	0,73	975,50	0,98			0,74	741,14	
12	NS8593	9	734	975	975	976	977	976	0,73	975,40	0,98			0,74	743,20	
12	NS8593	9	736	972	975	975	976	977	0,74	973,80	0,97			0,75	745,84	
12	NS8593	9	742	971	972	975	975	976	0,74	972,50	0,97			0,75	752,42	
12	NS8593	10	726	975	974	974	974	974	0,73	974,50	0,97	0,98	61,52	0,74	735,44	735,92
12	NS8593	10	726	976	975	974	974	974	0,73	975,20	0,98			0,74	735,17	
12	NS8593	10	728	976	976	975	974	974	0,73	975,50	0,98			0,74	737,09	
12	NS8593	10	728	976	976	976	975	974	0,73	975,70	0,98			0,74	737,01	
12	NS8593	10	726	976	976	976	976	975	0,73	975,90	0,98			0,73	734,91	
12	NS8593	11	728	974	975	971	970	1096	0,73	985,70	0,99	0,98	61,43	0,73	733,26	731,37
12	NS8593	11	726	974	974	975	971	970	0,73	973,40	0,97			0,74	735,85	
12	NS8593	11	720	975	974	974	975	971	0,72	974,30	0,97			0,73	729,43	
12	NS8593	11	720	975	975	974	974	975	0,72	974,80	0,97			0,73	729,25	
12	NS8593	11	720	976	975	975	974	974	0,72	975,30	0,98			0,73	729,06	
12	NS8593	12	740	1369	986	1053	918	973	0,74	1176,10	1,18	1,15	52,08	0,68	682,35	699,98
12	NS8593	12	752	1499	1369	986	1053	918	0,75	1319,00	1,32			0,65	654,78	
12	NS8593	12	766	1019	1499	1369	986	1053	0,77	1150,10	1,15			0,71	714,27	
12	NS8593	12	748	829	1019	1499	1369	986	0,75	1003,70	1,00			0,75	746,62	
12	NS8593	12	740	1114	829	1019	1499	1369	0,74	1111,50	1,11			0,70	701,90	
12	NS8593	13	798	1316	1323	1317	1313	1315	0,80	1317,10	1,32	1,32	45,54	0,70	695,33	684,07
12	NS8593	13	786	1316	1316	1323	1317	1313	0,79	1316,50	1,32			0,69	685,03	
12	NS8593	13	786	1318	1316	1316	1323	1317	0,79	1317,80	1,32			0,68	684,70	
12	NS8593	13	778	1318	1318	1316	1316	1323	0,78	1318,10	1,32			0,68	677,65	
12	NS8593	13	778	1319	1318	1318	1316	1316	0,78	1318,10	1,32			0,68	677,65	

Table 3 continued

13	Baseline anaesthesia	-5	690	1183	1107	1019	1064	1004	0,69	1121,60	1,12	1,06	56,53	0,65	651,52	651,18
13	Baseline anaesthesia	-5	672	1017	1183	1107	1019	1064	0,67	1064,10	1,06			0,65	651,45	
13	Baseline anaesthesia	-5	684	1006	1017	1183	1107	1019	0,68	1037,30	1,04			0,67	671,59	
13	Baseline anaesthesia	-5	658	1051	1006	1017	1183	1107	0,66	1057,40	1,06			0,64	639,89	
13	Baseline anaesthesia	-5	650	992	1051	1006	1017	1183	0,65	1026,80	1,03			0,64	641,46	
13	Baseline anaesthesia	-4	660	803	1055	1730	1105	1452	0,66	1041,20	1,04	1,08	55,52	0,65	646,81	636,53
13	Baseline anaesthesia	-4	642	860	803	1055	1730	1105	0,64	979,60	0,98			0,65	648,65	
13	Baseline anaesthesia	-4	660	1200	860	803	1055	1730	0,66	1130,80	1,13			0,62	620,66	
13	Baseline anaesthesia	-4	672	1220	1200	860	803	1055	0,67	1121,80	1,12			0,63	634,47	
13	Baseline anaesthesia	-4	672	1200	1220	1200	860	803	0,67	1130,30	1,13			0,63	632,08	
13	Baseline anaesthesia	-3	654	951	1093	1262	913	866	0,65	998,20	1,00	1,00	59,85	0,65	654,59	660,24
13	Baseline anaesthesia	-3	660	1236	951	1093	1262	913	0,66	1135,00	1,14			0,62	619,51	
13	Baseline anaesthesia	-3	674	992	1236	951	1093	1262	0,67	1073,80	1,07			0,65	650,43	
13	Baseline anaesthesia	-3	658	763	992	1236	951	1093	0,66	907,90	0,91			0,69	690,57	
13	Baseline anaesthesia	-3	650	854	763	992	1236	951	0,65	897,50	0,90			0,69	686,11	
13	Baseline anaesthesia	-2	660	922	1050	803	1061	954	0,66	952,80	0,95	0,97	61,65	0,68	676,15	667,58
13	Baseline anaesthesia	-2	678	976	922	1050	803	1061	0,68	963,80	0,96			0,69	690,62	
13	Baseline anaesthesia	-2	644	878	976	922	1050	803	0,64	911,70	0,91			0,67	674,47	
13	Baseline anaesthesia	-2	652	1253	878	976	922	1050	0,65	1096,90	1,10			0,62	622,54	
13	Baseline anaesthesia	-2	654	826	1253	878	976	922	0,65	941,20	0,94			0,67	674,12	
13	Baseline anaesthesia	-1	658	562	887	861	859	934	0,66	723,80	0,72	0,75	79,63	0,77	773,42	746,69
13	Baseline anaesthesia	-1	654	788	562	887	861	859	0,65	767,10	0,77			0,75	746,71	
13	Baseline anaesthesia	-1	644	675	788	562	887	861	0,64	726,10	0,73			0,76	755,77	
13	Baseline anaesthesia	-1	652	894	675	788	562	887	0,65	805,70	0,81			0,73	726,38	
13	Baseline anaesthesia	-1	631	727	894	675	788	562	0,63	744,80	0,74			0,73	731,16	
13	NS8593	1	734	808	919	1183	1035	873	0,73	896,90	0,90	0,88	68,12	0,78	775,04	780,69
13	NS8593	1	728	852	808	919	1183	1035	0,73	901,30	0,90			0,77	766,83	
13	NS8593	1	772	812	852	808	919	1183	0,77	867,40	0,87			0,83	828,91	
13	NS8593	1	732	853	812	852	808	919	0,73	846,80	0,85			0,80	795,46	
13	NS8593	1	696	947	853	812	852	808	0,70	891,30	0,89			0,74	737,22	
13	NS8593	2	720	906	826	578	869	970	0,72	859,90	0,86	0,80	74,87	0,78	776,44	754,77
13	NS8593	2	716	795	906	826	578	869	0,72	806,00	0,81			0,80	797,53	
13	NS8593	2	728	787	795	906	826	578	0,73	783,50	0,78			0,82	822,45	
13	NS8593	2	614	841	787	795	906	826	0,61	830,60	0,83			0,67	673,71	
13	NS8593	2	600	620	841	787	795	906	0,60	727,00	0,73			0,70	703,69	
13	NS8593	3	765	891	915	856	1106	1197	0,77	944,40	0,94	1,01	59,28	0,79	787,20	747,70

Table 3 continued

13	NS8593	3	734	1119	891	915	856	1106	0,73	1025,40	1,03			0,72	724,85	
13	NS8593	3	784	1150	1119	891	915	856	0,78	1065,00	1,07			0,76	759,70	
13	NS8593	3	740	859	1150	1119	891	915	0,74	952,00	0,95			0,76	758,43	
13	NS8593	3	734	1172	859	1150	1119	891	0,73	1073,80	1,07			0,71	708,33	
13	NS8593	4	728	737	1048	1322	668	821	0,73	859,20	0,86	1,00	60,06	0,79	785,39	763,98
13	NS8593	4	814	1320	737	1048	1322	668	0,81	1111,20	1,11			0,77	772,20	
13	NS8593	4	760	1036	1320	737	1048	1322	0,76	1092,70	1,09			0,73	727,05	
13	NS8593	4	740	959	1036	1320	737	1048	0,74	997,20	1,00			0,74	741,04	
13	NS8593	4	768	868	959	1036	1320	737	0,77	935,10	0,94			0,79	794,20	
13	NS8593	5	742	672	686	1176	908	1260	0,74	807,60	0,81	0,90	66,96	0,83	825,67	772,15
13	NS8593	5	722	941	672	686	1176	908	0,72	881,90	0,88			0,77	768,83	
13	NS8593	5	692	951	941	672	686	1176	0,69	917,10	0,92			0,72	722,60	
13	NS8593	5	722	707	951	941	672	686	0,72	773,60	0,77			0,82	820,88	
13	NS8593	5	758	1404	707	951	941	672	0,76	1099,80	1,10			0,72	722,79	
13	NS8593	6	694	910	1098	693	708	760	0,69	890,70	0,89	0,84	71,34	0,74	735,35	748,65
13	NS8593	6	666	758	910	1098	693	708	0,67	810,90	0,81			0,74	739,59	
13	NS8593	6	686	730	758	910	1098	693	0,69	786,70	0,79			0,77	773,43	
13	NS8593	6	698	960	730	758	910	1098	0,70	902,60	0,90			0,73	734,70	
13	NS8593	6	686	765	960	730	758	910	0,69	814,30	0,81			0,76	760,21	
13	NS8593	7	890	1947	1985	1974	1971	1974	0,89	1962,40	1,96	1,97	30,39	0,64	635,33	637,42
13	NS8593	7	894	1986	1947	1985	1974	1971	0,89	1975,40	1,98			0,64	636,08	
13	NS8593	7	898	1978	1986	1947	1985	1974	0,90	1976,80	1,98			0,64	638,70	
13	NS8593	7	896	1985	1978	1986	1947	1985	0,90	1979,90	1,98			0,64	636,78	
13	NS8593	7	900	1976	1985	1978	1986	1947	0,90	1976,10	1,98			0,64	640,23	
13	NS8593	8	888	2104	2119	2074	2124	2096	0,89	2105,20	2,11	2,10	28,53	0,61	612,02	616,74
13	NS8593	8	892	2110	2104	2119	2074	2124	0,89	2107,50	2,11			0,61	614,44	
13	NS8593	8	898	2107	2110	2104	2119	2074	0,90	2105,20	2,11			0,62	618,91	
13	NS8593	8	890	2124	2107	2110	2104	2119	0,89	2116,70	2,12			0,61	611,73	
13	NS8593	8	904	2049	2124	2107	2110	2104	0,90	2081,40	2,08			0,63	626,60	
13	NS8593	9	720	974	976	975	974	976	0,72	974,70	0,97	0,97	61,55	0,73	729,28	721,57
13	NS8593	9	714	974	974	976	975	974	0,71	974,30	0,97			0,72	723,36	
13	NS8593	9	710	970	974	974	976	975	0,71	972,30	0,97			0,72	720,04	
13	NS8593	9	708	976	970	974	974	976	0,71	974,40	0,97			0,72	717,24	
13	NS8593	9	710	982	976	970	974	974	0,71	978,00	0,98			0,72	717,94	
13	NS8593	10	712	972	974	975	975	975	0,71	973,30	0,97	0,97	61,54	0,72	721,70	715,42
13	NS8593	10	706	970	972	974	975	975	0,71	971,80	0,97			0,72	716,17	

Table 3 continued

13	NS8593	10	700	983	970	972	974	975	0,70	977,60	0,98			0,71	707,97	
13	NS8593	10	710	977	983	970	972	974	0,71	976,70	0,98			0,72	718,42	
13	NS8593	10	704	975	977	983	970	972	0,70	975,40	0,98			0,71	712,82	
13	NS8593	11	694	980	978	971	972	975	0,69	977,40	0,98	0,98	61,48	0,70	701,98	703,12
13	NS8593	11	698	975	980	978	971	972	0,70	975,60	0,98			0,71	706,67	
13	NS8593	11	695	974	975	980	978	971	0,70	974,90	0,97			0,70	703,89	
13	NS8593	11	702	976	974	975	980	978	0,70	976,10	0,98			0,71	710,54	
13	NS8593	11	684	975	976	974	975	980	0,68	975,60	0,98			0,69	692,50	
13	NS8593	12	858	1764	1774	1720	1848	1791	0,86	1772,70	1,77	1,77	33,96	0,64	644,42	645,20
13	NS8593	12	854	1775	1764	1774	1720	1848	0,85	1774,50	1,77			0,64	641,09	
13	NS8593	12	856	1758	1775	1764	1774	1720	0,86	1759,80	1,76			0,65	645,27	
13	NS8593	12	862	1742	1758	1775	1764	1774	0,86	1753,90	1,75			0,65	650,89	
13	NS8593	12	858	1790	1742	1758	1775	1764	0,86	1773,10	1,77			0,64	644,35	
13	NS8593	13	708	973	1329	1156	847	1366	0,71	1089,20	1,09	1,07	55,97	0,68	678,39	682,90
13	NS8593	13	680	780	973	1329	1156	847	0,68	917,80	0,92			0,71	709,80	
13	NS8593	13	710	1437	780	973	1329	1156	0,71	1220,30	1,22			0,64	642,72	
13	NS8593	13	720	1036	1437	780	973	1329	0,72	1113,60	1,11			0,68	682,29	
13	NS8593	13	708	986	1036	1437	780	973	0,71	1019,20	1,02			0,70	701,30	

Table 3 QTc and HR measurements and calculations of the unconscious study. Measurements and calculations were carried out before (baseline), during and after NS8593/flecainide infusion. The QT intervals of each of the six horses (horse 8 to 13) were measured on 5 consecutive beats within each recording period (time -5 to 13). Recording periods were just before drug administration (t=-1), and at 5 (t=-2), 10 (t=-3), 15 (t=-4), and 20 (t=-5) minutes before drug administration, immediately after starting drug administration (t=1), 1 (t=2), 2 (t=3), 3 (t=4), 4 (t=5), 5 (t=6), 10 (t=7), 15 (t=8), 20 (t=9), 25 (t=10), 30 (t=11), 45 (t=12), and 60 (t=13) minutes after drug administration. Horse 8 was euthanized during the procedure and only 13 recording periods (-5 to 8) were achieved from this horse. The RR intervals were likewise calculated on 5 consecutive beats where RRn-1 is the RR interval just previous to a QT interval, RRn-2 the second interval, RR-3 the third interval, RR-4 the fourth interval, and RR-5 the fifth interval. The modified RR interval (RRmod) was calculated using the RRmod formula (5*RRn-1 + 2*RRn-2 + RRn-3 +RRn-4 +RRn-5)/10), and a mean was calculated. The QTc intervals were calculated using Bazett's formula for correction (QTc=QT/√RRmod), and a mean for each recording period was calculated (QTc Bazett's mean). HR was calculated as 60/RRmod (mean).

Table 3 continued

Appendix B

Conscious study

Table Analyzed	QTc, Standing One Way ANOVA
Repeated Measures ANOVA	
P value	< 0.0001
P value summary	****
Are means signif. different? (P < 0.05)	Yes
Number of groups	18
F	5.466

Table 4 One Way ANOVA, QTc. One-way repeated-measures analysis of variance (ANOVA) was used to compare QTc intervals across treatment periods. Where the test statistic value indicated significant differences (P<0.0001), all pairwise comparisons were performed using Dunnett's multiple comparison test (see table 5).

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
Just before treatment vs 20 min pre treatment	35.24	1.275	No	ns	-45.61 to 116.1
Just before treatment vs 15 min pre treatment	-3.140	0.1137	No	ns	-83.99 to 77.70
Just before treatment vs 10 min pre treatment	22.69	0.8212	No	ns	-58.16 to 103.5
Just before treatment vs 5 min pre treatment	17.26	0.6248	No	ns	-63.58 to 98.11
Just before treatment vs Start treatment	26.67	0.9655	No	ns	-54.17 to 107.5
Just before treatment vs 1 min after	62.04	2.246	No	ns	-18.81 to 142.9
Just before treatment vs 2 min after	27.47	0.9944	No	ns	-53.37 to 108.3
Just before treatment vs 3 min after	-3.073	0.1112	No	ns	-83.92 to 77.77
Just before treatment vs 4 min after	10.86	0.3930	No	ns	-69.99 to 91.70
Just before treatment vs 5 min after	9.493	0.3436	No	ns	-71.35 to 90.34
Just before treatment vs 10 min after	-19.65	0.7112	No	ns	-100.5 to 61.20
Just before treatment vs 15 min after	-96.67	3.499	Yes	**	-177.5 to -15.82
Just before treatment vs 20 min after	-94.00	3.402	Yes	*	-174.8 to -13.15
Just before treatment vs 25 min after	-83.83	3.035	Yes	*	-164.7 to -2.989
Just before treatment vs 30 min after	-44.45	1.609	No	ns	-125.3 to 36.39
Just before treatment vs 45 min after	29.72	1.076	No	ns	-51.12 to 110.6
Just before treatment vs 60 min after	0.5771	0.02089	No	ns	-80.27 to 81.42

Table 5 Dunnett's multiple comparison test. Pairwise comparison of QTc mean values in the conscious study. QTc mean values at 15, 20 and 25 minutes (time: 8, 9 and 10, respectively) following infusion were significantly prolonged (P<0.05) when compared to the reference mean value. The reference mean value consisted of the QTc means just before drug treatment (time: -1). Mean Diff; mean difference, q; test q value; 95% CI off diff; 95% confidence intervals of difference.

Table Analyzed	QRS Standing One way ANOVA
Repeated Measures ANOVA	
P value	< 0.0001
P value summary	****
Are means signif. different? (P < 0.05)	Yes
Number of groups	18
F	6.963

Table 6 One Way ANOVA, QRS. One-way repeated-measures analysis of variance (ANOVA) was used to compare QRS intervals across treatment periods. Where the test statistic value indicated significant differences (P<0.0001), all pairwise comparisons were performed using Dunnett's multiple comparison test (see table 7).

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
Just before treatment vs 20 min pre treatment	2.800	0.7864	No	ns	-7.619 to 13.22
Just before treatment vs 15 min pre treatment	5.000	1.404	No	ns	-5.419 to 15.42
Just before treatment vs 10 min pre treatment	5.000	1.404	No	ns	-5.419 to 15.42
Just before treatment vs 5 min pre treatment	0.2667	0.07490	No	ns	-10.15 to 10.69
Just before treatment vs Start treatment	0.2000	0.05617	No	ns	-10.22 to 10.62
Just before treatment vs 1 min after	0.06667	0.01872	No	ns	-10.35 to 10.49
Just before treatment vs 2 min after	-2.400	0.6741	No	ns	-12.82 to 8.019
Just before treatment vs 3 min after	-0.8667	0.2434	No	ns	-11.29 to 9.552
Just before treatment vs 4 min after	-4.867	1.367	No	ns	-15.29 to 5.552
Just before treatment vs 5 min after	-3.867	1.086	No	ns	-14.29 to 6.552
Just before treatment vs 10 min after	-13.73	3.857	Yes	**	-24.15 to -3.315
Just before treatment vs 15 min after	-18.07	5.074	Yes	***	-28.49 to -7.648
Just before treatment vs 20 min after	-14.40	4.045	Yes	**	-24.82 to -3.981
Just before treatment vs 25 min after	-10.93	3.071	Yes	*	-21.35 to -0.5147
Just before treatment vs 30 min after	-6.133	1.723	No	ns	-16.55 to 4.285
Just before treatment vs 45 min after	-4.267	1.198	No	ns	-14.69 to 6.152
Just before treatment vs 60 min after	-1.133	0.3183	No	ns	-11.55 to 9.285

Table 7 Dunnett's multiple comparison test. Pairwise comparison of QRS mean values in the conscious study. QRS mean values at 10, 15, 20 and 25 minutes (time: 7, 8, 9 and 10, respectively) following infusion were significantly prolonged (P<0.05) when compared to the reference mean value. The reference mean value consisted of the QRS means just before drug treatment (time: -1). Mean Diff; mean difference, q; test q value; 95% CI off diff; 95% confidence intervals of difference.

Table Analyzed	JTc, Standing One Way ANOVA
Repeated Measures ANOVA	
P value	< 0.0001
P value summary	****
Are means signif. different? (P < 0.05)	Yes
Number of groups	18
F	3.586

Table 8 One Way ANOVA, JTc. One-way repeated-measures analysis of variance (ANOVA) was used to compare JTc intervals across treatment periods. Where the test statistic value indicated significant differences (P<0.0001), all pairwise comparisons were performed using Dunnett's multiple comparison test (see table 9).

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
Just before treatment vs 20 min pre treatment	24.01	1.050	No	ns	-42.89 to 90.91
Just before treatment vs 15 min pre treatment	-6.285	0.2749	No	ns	-73.19 to 60.62
Just before treatment vs 10 min pre treatment	10.93	0.4781	No	ns	-55.97 to 77.83
Just before treatment vs 5 min pre treatment	9.567	0.4185	No	ns	-57.33 to 76.47
Just before treatment vs Start treatment	24.78	1.084	No	ns	-42.12 to 91.68
Just before treatment vs 1 min after	47.48	2.077	No	ns	-19.42 to 114.4
Just before treatment vs 2 min after	24.18	1.058	No	ns	-42.72 to 91.08
Just before treatment vs 3 min after	-3.808	0.1666	No	ns	-70.71 to 63.09
Just before treatment vs 4 min after	8.525	0.3729	No	ns	-58.38 to 75.43
Just before treatment vs 5 min after	4.284	0.1874	No	ns	-62.62 to 71.18
Just before treatment vs 10 min after	-15.01	0.6567	No	ns	-81.91 to 51.89
Just before treatment vs 15 min after	-64.64	2.827	No	ns	-131.5 to 2.260
Just before treatment vs 20 min after	-54.33	2.377	No	ns	-121.2 to 12.57
Just before treatment vs 25 min after	-55.18	2.414	No	ns	-122.1 to 11.72
Just before treatment vs 30 min after	-28.15	1.231	No	ns	-95.05 to 38.75
Just before treatment vs 45 min after	22.47	0.9831	No	ns	-44.43 to 89.38
Just before treatment vs 60 min after	-2.704	0.1183	No	ns	-69.60 to 64.20

Table 9 Dunnett's multiple comparison test. Pairwise comparison of JTc mean values in the conscious study. No JTc mean value was significantly different (P>0.05) from reference mean value. The reference mean value consisted of the JTc means just before drug treatment (time: -1). Mean Diff; mean difference, q; test q value; 95% CI off diff; 95% confidence intervals of difference.

Table Analyzed	HR over time, Standing One Way ANOVA
Repeated Measures ANOVA	
P value	< 0.0001
P value summary	****
Are means signif. different? (P < 0.05)	Yes
Number of groups	18
F	4.850

Table 10 One Way ANOVA, HR. One-way repeated-measures analysis of variance (ANOVA) was used to compare heart rates (HR) over time. Where the test statistic value indicated significant differences (P<0.0001), all pairwise comparisons were performed using Dunnett's multiple comparison test (see table 11).

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
Just before treatment vs 20 min pre treatment	6.307	1.201	No	ns	-9.062 to 21.68
Just before treatment vs 15 min pre treatment	-0.4995	0.09511	No	ns	-15.87 to 14.87
Just before treatment vs 10 min pre treatment	5.564	1.059	No	ns	-9.805 to 20.93
Just before treatment vs 5 min pre treatment	4.557	0.8678	No	ns	-10.81 to 19.93
Just before treatment vs Start treatment	0.4358	0.08298	No	ns	-14.93 to 15.80
Just before treatment vs 1 min after	10.19	1.940	No	ns	-5.177 to 25.56
Just before treatment vs 2 min after	3.949	0.7520	No	ns	-11.42 to 19.32
Just before treatment vs 3 min after	0.2234	0.04253	No	ns	-15.15 to 15.59
Just before treatment vs 4 min after	3.551	0.6761	No	ns	-11.82 to 18.92
Just before treatment vs 5 min after	5.079	0.9671	No	ns	-10.29 to 20.45
Just before treatment vs 10 min after	3.835	0.7302	No	ns	-11.53 to 19.20
Just before treatment vs 15 min after	-11.84	2.255	No	ns	-27.21 to 3.524
Just before treatment vs 20 min after	-20.05	3.817	Yes	**	-35.41 to -4.677
Just before treatment vs 25 min after	-14.02	2.670	No	ns	-29.39 to 1.344
Just before treatment vs 30 min after	-9.121	1.737	No	ns	-24.49 to 6.247
Just before treatment vs 45 min after	6.649	1.266	No	ns	-8.719 to 22.02
Just before treatment vs 60 min after	2.565	0.4884	No	ns	-12.80 to 17.93

Table 11 Dunnett's multiple comparison test. Pairwise comparison of HR mean values in the conscious study. HR mean values at 20 minutes following infusion were significantly increased (P<0.05) when compared to the reference mean value. The reference mean value consisted of the HR means just before drug treatment (time: -1). Mean Diff; mean difference, q; test q value; 95% CI off diff; 95% confidence intervals of difference.

Unconscious study

Table Analyzed	QTc, anesthesia, NS8593, One Way ANOVA
Repeated Measures ANOVA	
P value	0.2241
P value summary	ns
Are means signif. different? (P < 0.05)	No
Number of groups	18
F	1.311

Table 12 One Way ANOVA, QTc. One-way repeated-measures analysis of variance (ANOVA) was used to compare QTc intervals across treatment periods. No significant differences (P>0.0001) was found between QTc mean values.

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
Just before treatment vs 20 min pre treatment	36.81	1.115	No	ns	-61.34 to 135.0
Just before treatment vs 15 min pre treatment	41.41	1.254	No	ns	-56.74 to 139.6
Just before treatment vs 10 min pre treatment	39.44	1.194	No	ns	-58.71 to 137.6
Just before treatment vs 5 min pre treatment	30.06	0.9102	No	ns	-68.09 to 128.2
Just before treatment vs Start treatment	14.31	0.4334	No	ns	-83.84 to 112.5
Just before treatment vs 1 min after	48.47	1.468	No	ns	-49.68 to 146.6
Just before treatment vs 2 min after	28.27	0.8562	No	ns	-69.88 to 126.4
Just before treatment vs 3 min after	39.62	1.200	No	ns	-58.53 to 137.8
Just before treatment vs 4 min after	30.63	0.9275	No	ns	-67.52 to 128.8
Just before treatment vs 5 min after	42.80	1.296	No	ns	-55.35 to 141.0
Just before treatment vs 10 min after	58.98	1.786	No	ns	-39.17 to 157.1
Just before treatment vs 15 min after	-3.062	0.09273	No	ns	-101.2 to 95.09
Just before treatment vs 20 min after	-6.296	0.1906	No	ns	-104.4 to 91.85
Just before treatment vs 25 min after	-29.31	0.8875	No	ns	-127.5 to 68.84
Just before treatment vs 30 min after	-31.41	0.9510	No	ns	-129.6 to 66.74
Just before treatment vs 45 min after	37.96	1.149	No	ns	-60.19 to 136.1
Just before treatment vs 60 min after	-1.830	0.05542	No	ns	-99.98 to 96.32

Table 13 Dunnett's multiple comparison test. Pairwise comparison of QTc mean values in the unconscious study. No QTc mean value was significantly different (P>0.05) from reference mean value. The reference mean value consisted of the QTc means just before drug treatment (time: -1). Mean Diff; mean difference, q; test q value; 95% CI off diff; 95% confidence intervals of difference.

Table Analyzed	HR over time, Anaesthesia One Way ANOVA
Repeated Measures ANOVA	
P value	0.0990
P value summary	ns
Are means signif. different? (P < 0.05)	No
Number of groups	18
F	1.601

Table 14 One Way ANOVA, HR. One-way repeated-measures analysis of variance (ANOVA) was used to compare heart rate (HR) values over time. No significant differences (P>0.0001) were found between HR mean values.

Dunnett's Multiple Comparison Test	Mean Diff.	q	Significant? P < 0.05?	Summary	95% CI of diff
Just before treatment vs 20 min pre treatment	3.515	0.4487	No	ns	-19.77 to 26.80
Just before treatment vs 15 min pre treatment	3.512	0.4483	No	ns	-19.77 to 26.80
Just before treatment vs 10 min pre treatment	5.670	0.7238	No	ns	-17.61 to 28.95
Just before treatment vs 5 min pre treatment	1.061	0.1354	No	ns	-22.22 to 24.34
Just before treatment vs Start treatment	2.149	0.2743	No	ns	-21.13 to 25.43
Just before treatment vs 1 min after	6.262	0.7994	No	ns	-17.02 to 29.55
Just before treatment vs 2 min after	6.150	0.7851	No	ns	-17.13 to 29.43
Just before treatment vs 3 min after	8.679	1.108	No	ns	-14.60 to 31.96
Just before treatment vs 4 min after	4.573	0.5838	No	ns	-18.71 to 27.86
Just before treatment vs 5 min after	3.812	0.4866	No	ns	-19.47 to 27.10
Just before treatment vs 10 min after	7.008	0.8946	No	ns	-16.28 to 30.29
Just before treatment vs 15 min after	-1.533	0.1957	No	ns	-24.82 to 21.75
Just before treatment vs 20 min after	-11.97	1.528	No	ns	-35.26 to 11.31
Just before treatment vs 25 min after	-12.97	1.656	No	ns	-36.25 to 10.31
Just before treatment vs 30 min after	-12.00	1.532	No	ns	-35.29 to 11.28
Just before treatment vs 45 min after	1.107	0.1413	No	ns	-22.18 to 24.39
Just before treatment vs 60 min after	10.62	1.356	No	ns	-12.66 to 33.90

Table 15 Dunnett's multiple comparison test. Pairwise comparison of HR mean values in the unconscious study. A non-significant (P>0.05) increase in HR mean values was observed at 20, 25 and 30 minutes following infusion. The reference mean value consisted of the HR means just before drug treatment (time: -1). Mean Diff; mean difference, q; test q value; 95% CI off diff; 95% confidence intervals of difference.