Comparison of non-invasive and implanted telemetric measurement of blood pressure and electrocardiogram in conscious beagle dogs

Gemma Ward *, Phil Milliken, Bela Patel, Nick McMahon

Department of Safety Pharmacology, GlaxoSmithKline, Park Road, Ware, SG12 0DP, UK

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A B S T R A C T

Introduction: The objective of this study was to evaluate the ability of a non-invasive telemetry monitoring system to detect and quantify changes in blood pressure and electrocardiogram (ECG) parameters in response to vehicle, l-NAME or minoxidil administration to freely moving beagle dogs. Data from a non-invasive telemetry monitoring system were compared to data captured from an invasive telemetry implant in the same animals. Methods: Blood pressure and ECG data were simultaneously acquired from male dogs using a non-invasive and an invasive implanted telemetry system for 2 hours predose and 24 hours post dosing with vehicle (n = 5), minoxidil at 1 mg/kg (n = 4) and L-NAME at 10 mg/kg (n = 5) on separate test days. Values for mean blood pressure, systolic blood pressure, diastolic blood pressure, pulse pressure, heart rate, RR, PR, QRS, QT and QTcL (heart rate corrected QT interval) interval were reported for both methods. Results: Statistically significant reductions in blood pressure and pulse pressure and increases in heart rate, with associated ECG interval changes were apparent following dosing with l-NAME when using the invasive telemetry system, changes were apparent when using the non-invasive telemetry system, however, no change was apparent for pulse pressure, they were of shorter duration and not statistically significant. Statistically significant decreases in heart rate, with associated changes in ECG intervals, were apparent following treatment with l-NAME for both invasive and non-invasive methods. Discussion: This study shows that the non-invasive system can be successfully used to acquire both ECG and blood pressure data in freely moving jacketed dogs for at least 26 hours, yet requires further technique refinement to improve system sensitivity to detect smaller changes in blood pressure.

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1. Introduction

Systemic arterial blood pressure is a fundamental cardiovascular parameter used in preclinical and clinical settings to monitor haemodynamic status. It is determined as the product of cardiac output and systemic vascular resistance and is controlled by highly complex and dynamic status. It is determined as the product of cardiac output and systemic vascular resistance and is controlled by highly complex and dynamic mechanisms to maintain a pressure level to ensure adequate tissue perfusion and oxygenation. Drug-induced changes in arterial blood pressure can be characterised as hypotensive or hypertensive in nature and have been reported for drugs from a wide range of therapeutic classes (Breckenridge, 1979; Murphy & Dargie, 2007; Raj, Stein, Saavedra, & Roden, 2009). Hypertensive changes will increase after-load on the ventricles and can contribute to heart failure (Slørdal & Spigset, 2006) and can increase strain in end-}

Abbreviations: ECG, electrocardiogram; NIBP, non-invasive blood pressure; QTcL, QT interval duration corrected for changes in heart rate using an individual regression method.

* Corresponding author at: Department of Safety Pharmacology, GlaxoSmithKline R&D, Park Road, Ware, Hertfordshire, SG12 0DP, UK. Tel.: +44 1992502401.
E-mail address: gemma.lward@gsk.com (G. Ward).

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pressure, however, is rarely included in repeat dose toxicology studies. Methods are available to acquire blood pressure from dogs using minimally invasive direct measurement such as ear artery puncture (McMahon, Pollard, Hammond, & Valentin, 2007) or via an implanted miniature telemetry transmitter (McMahon, Mitchell, Klein, Jenkins, & Sarazan, 2010) or non-invasively via oscillometric cuff systems (Mitchell, McMahon, Beck, & Dustan Sarazan, 2010). The foregoing methods have limitations that may preclude wide-spread routine use in toxicology studies, thus a non-invasive method for acquisition of ambulatory blood pressures with acceptable precision to describe drug-induced changes in systolic, diastolic and mean arterial blood pressure is required.

The objective of this study was to evaluate a non-invasive telemetry monitoring system for detecting and quantifying changes in blood pressure, ECG and heart rate in response to vehicle and reference compounds given to conscious freely moving telemetered beagle dogs. Non-invasive telemetry data were compared to data simultaneously captured from the same animals implanted with an invasive telemetry device. The test compounds selected were NG-nitro-L-arginine methyl ester (L-NAME), a nonselective inhibitor of nitric oxide synthase, known to produce a long lasting pressor response and minoxidil, an ATP-sensitive potassium channel opener, a potent orally active hypotensive agent, the main mechanism of action being relaxation of the peripheral vascular smooth muscle.
was shaved and an oscillometric cuff was placed around the shaved torso. The ECG leads were attached to the transmitter carried in the place with a adhesive pre-gelled surface ECG electrodes (3 M Red Dot™, USA). On the day of recording the ECG electrodes were carefully applied to the jackets (Lomir, Biomedical INC, USA) required to carry the non-invasive telemetry pack (EMKA Pack, EMKA Technologies, France) by to clean skin and connected to multi-derivative ECG leads held in place with Velcro. For each dog when standing on four legs the cuff was approximately at the level of the heart. Each dog was returned to a pen equipped with telemetry receivers (DSI and EMKA) and the signals were observed for signal strength, morphology (ECG) and pulse amplitude (blood pressure), with adjustments made as necessary to optimise signal quality.

Dogs were housed singly during data acquisition and were group housed between these times throughout the study. Environmental controls were set to maintain temperature at 19±2 °C in the holding bay in which there was a 12-hour light/12-hour dark cycle and relative humidity range of 40% to 70%. Dogs were fed Harlan Teklad 2021C Dog Maintenance diet and provided with Sawdust and paper bedding (Datesand, UK). Filtered mains water as available ad-libitum.

2. Methods

All animals were treated in accordance to UK Home Office regulations (Animals (Scientific Procedures) Act 1986: London: Her Majesty’s Stationery Office 1986) and experimental protocols were reviewed and approved by GlaxoSmithKline ethical review.

2.1. Animals and surgical preparation

Five male beagle dogs, supplied by Harlan UK were instrumented under isoflurane anaesthesia with a telemetry transmitter (model number TL11M2-D70-PCT, Data Sciences International (DSI), St. Paul, MN, USA). The transmitter was placed in an intramuscular pocket in the lower abdomen, with the fluid filled catheter inserted into the femoral artery and advanced so that the catheter tip was in the abdominal aorta for measurement of arterial blood pressure and leads were placed on the base and apex of the pericardium to measure ECG. Dogs were allowed to recover for a minimum of 4 weeks prior to use on studies, 1 dog had been previously used on Safety Pharmacology studies with at least a 7 week washout between studies and 4 dogs were naïve. On the first day of study the dogs were 1.4 to 3.8 years old and in the weight range of 11.5 to 15.2 kg.

Prior to the first data acquisition session, all dogs were acclimatised to the jackets (Lomir, Biomedical INC, USA) required to carry the non-invasive telemetry pack (EMKA Pack, EMKA Technologies, France) by gradually increasing the time in jackets from 1 to 24 hours over a 3 day period. Approximately 48 hours prior to the recording days the dogs were shaved on the torso to allow for the application of self adhesive pre-gelled surface ECG electrodes (3 M Red Dot™, 3 M plc, UK). On the day of recording the ECG electrodes were carefully applied to clean skin and connected to multi-derivative ECG leads held in place with a fitted t-shirt (Lomir, Biomedical INC, USA) covering the torso. The ECG leads were attached to the transmitter carried in the jacket placed over the t-shirt.

To acquire non-invasive arterial blood pressure the base of the tail was shaved and an oscillometric cuff was placed around the shaved portion. The oscillometric cuff was attached by tubing to the telemetry transmitter and held in place with a stopper of bandage and self-adhesive surgical tape (3 M Micropore™ or 3 M Vetrap™). A fabric cover was placed over the oscillometric cuff and secured to the jacket with Velcro. For each dog when standing on four legs the cuff was approximately at the level of the heart. Each dog was returned to a pen equipped with telemetry receivers (DSI and EMKA) and the signals were observed for signal strength, morphology (ECG) and pulse amplitude (blood pressure), with adjustments made as necessary to optimise signal quality.

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2.2. Compound and dose preparation

Minoxidil and N-Nitro-L-Arginine Methyl Ester Hydrochloride (L-NAME) were supplied by Sigma Aldrich. Oral suspension formulation at a concentration of 1 mg/mL Minoxidil in 0.5% (w/v) aqueous methylcellulose containing 0.1% (w/v) Tween 80 was prepared just prior to dosing. Capsule formulation at L-NAME dose of 10 mg/kg was prepared up to 1 day prior to dosing using the most recent bodyweight. Using a cross-over design (Table 1) each dog received vehicle (n = 5), oral gavage dose of Minoxidil at 1 mg/kg (n = 4) and a capsule dose of L-NAME at 10 mg/kg (n = 5) on separate test days.

2.3. Data acquisition and analysis

Invasive and non-invasive telemetry recordings were captured by EMKA IOX (EMKA Technologies) and analysed using EMKA ECG AUTO (EMKA Technologies). For invasive telemetry the data acquisition frequencies were 500 Hz for ECG and 250 Hz for blood pressure and for non-invasive telemetry the data acquisition frequency was 500 Hz for ECG and blood pressure. ECG (multi-lead for non-invasive and Lead II for invasive) and arterial blood pressure (invasive only) were captured continuously, for non-invasive arterial blood pressure the tail cuff was programmed to inflate and measure blood pressure at 3 minute intervals during a 2 hour predose and 24 hour post dose experimental period. During each inflation/deflation cycle of the tail-cuff a raw blood pressure amplitude signal is recorded. The signal is processed using a detection algorithm in order to derive values for systolic, diastolic and mean blood pressure for each cycle with pulse pressure calculated as the difference between systolic and diastolic pressures. A shape recognition algorithm excludes invalid pressure pulses for example pulses distorted due to movement artifact (Fig. 1).

<table>
<thead>
<tr>
<th>Study design.</th>
<th>Dog</th>
<th>Treatment order</th>
<th>L-NAME</th>
<th>Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle</td>
<td>L-NAME</td>
<td>Minoxidil</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>L-NAME</td>
<td>Minoxidil</td>
<td>Vehicle</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Vehicle</td>
<td>L-NAME</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Vehicle</td>
<td>Minoxidil</td>
<td>L-NAME</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>L-NAME</td>
<td>Vehicle</td>
<td>Minoxidil</td>
<td></td>
</tr>
</tbody>
</table>

(Gelzer & Ball, 1997; Hanton, Gautier, & Bonnet, 2004; Humphrey & Zins, 1984; Taylor, Patel, & Sullivan, 2007).

Table 1

<table>
<thead>
<tr>
<th>Dog Treatment order</th>
<th>L-NAME</th>
<th>Minoxidil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle</td>
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<td>-</td>
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<td>Vehicle</td>
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Two methods were used in this study: invasive and non-invasive. Invasive telemetry was achieved by placing a tygon catheter in the abdominal aorta for measurement of arterial blood pressure and leads for ECG and blood pressure. ECG (multi-lead for non-invasive and Lead II for invasive) and arterial blood pressure (invasive only) were captured continuously, for non-invasive arterial blood pressure the tail cuff was programmed to inflate and measure blood pressure at 3 minute intervals during a 2 hour predose and 24 hour post dose experimental period. During each inflation/deflation cycle of the tail-cuff a raw blood pressure amplitude signal is recorded. The signal is processed using a detection algorithm in order to derive values for systolic, diastolic and mean blood pressure for each cycle with pulse pressure calculated as the difference between systolic and diastolic pressures. A shape recognition algorithm excludes invalid pressure pulses for example pulses distorted due to movement artifact (Fig. 1).

Table 2

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Method</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Pulse pressure (mm Hg)</th>
<th>Heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minoxidil 1 mg/kg</td>
<td>Invasive</td>
<td>117±3</td>
<td>151±6</td>
<td>98±2</td>
<td>54±8</td>
<td>94±2</td>
</tr>
<tr>
<td>(n = 2 to 4)</td>
<td>Non-Invasive</td>
<td>96±4</td>
<td>116±5</td>
<td>75±2</td>
<td>41±4</td>
<td>76±2</td>
</tr>
<tr>
<td>L-NAME 10 mg/kg</td>
<td>Invasive</td>
<td>118±3</td>
<td>155±8</td>
<td>98±3</td>
<td>57±8</td>
<td>106±7</td>
</tr>
<tr>
<td>(n = 3 to 5)</td>
<td>Non-Invasive</td>
<td>94±2</td>
<td>113±3</td>
<td>74±2</td>
<td>39±2</td>
<td>85±2</td>
</tr>
</tbody>
</table>

Maximum change from predose

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Method</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Pulse pressure (mm Hg)</th>
<th>Heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minoxidil 1 mg/kg</td>
<td>Invasive</td>
<td>−42±1</td>
<td>−57±2</td>
<td>−37±1</td>
<td>−23±3</td>
<td>101±13</td>
</tr>
<tr>
<td>(n = 2 to 4)</td>
<td>Non-Invasive</td>
<td>−36±2</td>
<td>−40±2</td>
<td>−31±3</td>
<td>−13±2</td>
<td>102±1</td>
</tr>
<tr>
<td>L-NAME 10 mg/kg</td>
<td>Invasive</td>
<td>25±3</td>
<td>30±4</td>
<td>24±2</td>
<td>13±3</td>
<td>−34±7</td>
</tr>
<tr>
<td>(n = 3 to 5)</td>
<td>Non-Invasive</td>
<td>17±4</td>
<td>19±5</td>
<td>12±3</td>
<td>7±4</td>
<td>−28±1</td>
</tr>
</tbody>
</table>

Statistically significant differences in baseline values for mean, systolic, diastolic blood pressure, pulse pressure and heart rate, p-values < 0.05.
Heart rate corrected QT interval was calculated, using individual animal linear correction (QTcL) based on QT and heart rate data from a pre-treatment or vehicle data capture. The correction was calculated using the formula, QTcL = QT - \[b(\text{HR} - 60)\], where \(b\) is an individual correction factor taken from the equation describing the QT/HR relationship \(y = a + bx\).

2.4. Data and statistical analysis

Group mean and standard error of the mean (SEM) values averaged over 1 hour for mean blood pressure, systolic blood pressure, diastolic blood pressure, pulse pressure, heart rate, RR, PR and QT interval and QRS complex duration are reported for both telemetry methods.

Data were analysed for each method separately. All parameters were analysed at every averaged time-point using an Analysis of Covariance, with the pre-dose mean as a covariate and the factor being Treatment group. A Dunnett’s t-test (Dunnett, 1955) was run to compare the two treatment groups (Minoxidil and L-NAME) with vehicle, with \(p<0.05\) taken to indicate statistical significance. In addition, baseline values for blood pressures and heart rate obtained via the two telemetry techniques were compared using the paired Student’s t test, with \(p<0.05\) taken to indicate significance.

The correlation between values for mean, systolic, diastolic blood pressure, pulse pressure, heart rate and ECG intervals (RR, PR, QRS, QT, QTcL) was determined to compare data from the non-invasive and invasive (DSI) systems. Pairs of data points \((n = 78)\) from predose and all treatment period time points (vehicle \((n = 26)\), minoxidil \((n = 26)\) and L-NAME \((n = 26)\) were plotted. Statistical significance was obtained from the plotted linear line and a line of unity was added.

3. Results

3.1. Predose baseline haemodynamic and heart rate value

Statistically significant differences in predose values for mean, systolic, diastolic blood pressure, pulse pressure and heart rate recorded over 2 hours prior to treatment were observed between invasive and non-invasive methods, with non-invasive values consistently lower than invasive values (Table 2).

3.2. Effects of minoxidil on blood pressure and ECG in conscious dogs

Oral administration of minoxidil at 1 mg/kg was well tolerated in all animals \((n = 4)\), with no adverse clinical signs observed. Statistically significant reductions in mean, systolic and diastolic blood pressure were apparent for both telemetry systems following dosing with minoxidil, and due to a larger reduction in systolic pressure a reduction in pulse pressure was also observed (Fig. 2). Statistically significant increases in heart rate were apparent following treatment with minoxidil and due to this increase in heart rate there were concomitant reductions in RR, PR and QT intervals. There were no effects on QTcL interval. Changes in mean and diastolic blood pressure and heart rate were similar in duration and magnitude for both systems and still apparent up to 24 hours following dosing. Changes in systolic pressure and pulse pressure are similar in duration but larger in magnitude for the invasive telemetry system. QRS interval duration was shown to be reduced (maximum effect 8 msec) for the non-invasive system whereas no change was observed for invasive telemetry; however this change was not statistically significant.

![Fig. 3. Time course of change from predose for mean blood pressure (mmHg), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg) and pulse pressure (mm Hg), for the invasive (DSI) and non-invasive telemetry (NI) systems following oral administration of 10 mg/kg L-NAME or vehicle in conscious dogs. Data expressed as mean ± SEM, \(n = 3, 4\) or \(5\) per timepoint. Statistically significant changes were detected for mean blood pressure for invasive signals only, \(p\)-value < 0.05.](image-url)
3.3. Effects of L-NAME on blood pressure and ECG in conscious dogs

Oral administration of L-NAME at 10 mg/kg was well tolerated in all animals (n = 5), with no adverse clinical signs observed. Statistically significant increases in mean, systolic and diastolic blood pressure were apparent following dosing with L-NAME for invasive telemetry data, whereas increases in blood pressure determined from the non-invasive data were of shorter duration and did not reach statistical significance. An increase in pulse pressure was only detected following treatment with L-NAME with the invasive telemetry system (Fig. 3). Statistically significant decreases in heart rate were apparent following treatment with L-NAME for both invasive and non-invasive methods, due to this reduction in heart rate, increases in RR, PR and QT intervals were observed. There were no effects on QRS and QTcL interval.

3.4. Correlation between the non-invasive and invasive telemetry systems

The correlation between the blood pressure parameters (mean, systolic, diastolic and pulse pressure) and ECG parameters (heart rate, RR, PR, QRS, QT and QTcL interval) determined by each system is shown in Figs. 4 and 5. All of the individual data points (n = 78 pairs) from vehicle, minoxidil and L-NAME treatment periods are plotted on each graph. The line of unity and the linear correlation is shown on each graph. Statistically significant correlations were found between all parameters for both blood pressure and ECG intervals (p < 0.0001).

4. Discussion

The objective of this study was to evaluate the ability of a non-invasive telemetry monitoring system for detecting and quantifying changes in both blood pressure and electrocardiogram (ECG) parameters. This study compared the abilities of a non-invasive telemetry system and a ‘gold-standard’ invasive (fully implanted) telemetry system in conscious freely moving beagle dogs to detect drug-induced cardiovascular changes following administration of L-NAME and minoxidil. In previous studies, non-invasive telemetry systems for ECG monitoring and evaluation have been successfully used to detect drug induced changes in ECG parameters and the use of these systems is becoming more widespread in ambulatory dog safety studies (Chui et al., 2009; Prior et al., 2009).

Minoxidil is a potent vasodilator and relaxes smooth muscle by selectively increasing the membrane permeability to potassium ions (Hanton et al., 2004; Humphrey & Zins, 1984). In this study, as expected, minoxidil at 1 mg/kg was shown to reduce blood pressure and pulse pressure and increase heart rate. These effects were
detected by both the non-invasive and invasive telemetry methods; all changes were statistically significant for both systems and similar in magnitude and duration for mean and diastolic blood pressure. Changes in systolic blood pressure and pulse pressure were similar in duration but of larger magnitude for the invasive telemetry system, this may be due to sensitivity differences between the methods with the invasive method having a wider detection range than the non-invasive system, the difference may reflect differences in pressure response between the central invasive measurement and the peripheral non-invasive measurement. For non-invasive ECG signals only QRS interval was shown to reduce by up to 8 msec when no change was seen with the invasive telemetry system; however this change was not statistically significant. QRS interval was shown to be longer in duration and more variable when measured with the non-invasive system as reported previously (Prior et al., 2009). A number of factors may account for this difference including variable waveform morphology.

Fig. 5. Correlation between heart rate, RR, PR, QRS, QT and QTc interval derived from the invasive and non-invasive telemetry systems in conscious dogs, n = 78 data points. Dotted line is the line of unity. Statistically significant correlations were obtained for all intervals, p < 0.0001.
when using surface electrodes, different ECG lead positions and more difficulty in marking the QRS waveform consistently within the data capture system. L-NAME is a nonselective inhibitor of nitric oxide synthase, known to produce a long lasting pressor response (Gelzer and Ball, 1997). In this study L-NAME at 10 mg/kg was shown to increase blood pressure and pulse pressure and to reduce heart rate. These effects were detected by both the invasive and the non-invasive systems, however different magnitude and duration of effects were observed. The non-invasive telemetry system only detected changes in blood pressure up to approximately 7 hours post dosing compared to up to 21 to 24 hours post dosing for the invasive telemetry system, the changes observed were statistically significant for the invasive system only. In addition, no change in pulse pressure was detected with the non-invasive telemetry system compared to a change being detected up to 24 hours post dosing with the implanted invasive telemetry system. It is possible that these differences in magnitude and duration of effect are due to the loss of blood pressure signal when using the non-invasive telemetry system, with reduced n numbers being observed on occasion. However, the differences in detection may also be due to the sensitivity of the non-invasive system and this needs to be further investigated with the testing of other pressor agents to establish if this difference is due to methodology or pharmacology.

The use of a non-invasive telemetry system for measuring both ECG and blood pressure in this study has overcome a number of limitations of previous methods of measuring blood pressure with a tail-cuff device. Firstly, the system records both ECG and blood pressure signals simultaneously in the same animal using the same data capture system, secondly the system can be used in conscious freely moving animals housed in their home pens and finally the system was used for up to 26 hours in this study, therefore allowing data capture over extended time periods. Dogs were found to acclimatise quickly to the jackets, t-shirts and tail-cuffs worn during data capture. The average success rate for the number of valid blood pressure measurements out of the total recordings taken over 26 hours was 54%. This is a limitation of the system with the loss of non-invasive blood pressure data being due to signal drop out, loss or loosening of tail-cuff from the tail, poor signal quality due to noise caused by movement or poor signal amplitude. A further limitation of this system was on one occasion an animal was shown to have reduced use of the tail following application of the tail cuff, however this fully recovered. Additional refinements to the application of the tail-cuff are required to prevent the loss of tail movement observed in one animal and to increase the success rate of valid measurements to further improve the ability of the system to detect changes in blood pressure. These refinements could include modifications to the placement of the tail cuff, improvements in the detection of the signal by the software and changes to the frequency and number of measurements taken with the blood pressure cuff. It was noted that lower absolute values are obtained for mean, systolic and diastolic pressure when measured with the non-invasive blood pressure system, however this may be due to a number of factors such as the measurements being taken from the caudal artery in the tail compared with the abdominal aorta for the implanted catheter and a difference in pressure detection between the direct and indirect techniques. With the non-invasive method blood pressure derived heart rate values were also found to be lower; it is possible this is due to the non-invasive method only taking a single measurement every 3 minutes and the exclusion of noisy, possibly higher heart rate, data by the software compared to continuous data capture when using invasive telemetry.

The data in this study show that the oscillometric cuff method applied to freely moving dogs can be used to detect changes in blood pressure when compared to an invasive telemetry system. The system can be used successfully to acquire both ECG and blood pressure data in the same freely moving dogs for at least 26 hours. With some refinement to the technique to improve tail cuff application and signal quality, it is thought that the sensitivity of the system to detect smaller changes in blood pressure would improve.

The integration of safety pharmacology cardiovascular endpoints into early toxicology studies would bring scientific, practical and ethical benefits, however for blood pressure parameters the current methodologies have limitations, in particular requiring restraint during data acquisition and recordings limited to ‘snap-shots’ over the period of drug exposure (Bosiack, Mann, Dodam, Wagner-Mann, & Branson, 2010; Mitchell et al., 2010). This study has demonstrated that blood pressure can be recorded from ambulatory dogs using a non-invasive method and that this technique is able to follow drug-induced changes in blood pressure. Furthermore, the method can be easily coupled with ECG assessment; however, it requires further optimisation to improve the accurate detection of blood pressure changes before realising the goal of enhancing non clinical cardiovascular risk assessment.

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References


