Evaluation of a Non-Invasive Telemetry Method for Determining Blood Pressure in Dogs

Brandon Borders, Brian Roche, Tom Vinci, Shawnda Armentrout, Jeremy Smith, Steve Behringer, Ernesto Gonzalez, Brandon Wood, and Craig Hassler

Safety Pharmacology, Health and Life Sciences Global Business (HLSGB), Battelle, Columbus, OH

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ABSTRACT

The "gold standard" or industry standard for accurate collection of systemic arterial blood pressure in a cardiovascular safety pharmacology study uses a catheter attached to a telemetry device that is surgically implanted into a branch of the arterial tree. This invasive procedure, coupled with ECG collection, allows for new chemical entities to be evaluated for cardiovascular effects in compliance with ICH S7A guidelines. Attempts to meet ICH S7A guidelines with non-invasive telemetry devices have been periodically made with varying degrees of success. Recently developed devices incorporate the data collection systems into ambulatory jacketed systems that have the capability to transmit the data, thus incorporating some of the advantages of the implantable telemetry systems without surgical invasion. However, they are limited in the duration over which data can be continuously collected. The purpose of this study was to evaluate the functionality of a commercially available (EMKA) non-invasive telemetry jacket for collection of blood pressure in dogs. Four telemetered beagle dogs were instrumented with vascular access ports and acclimated to jackets prior to dosing. Dogs were intravenously dosed with an ambulatory infusion device with one of three treatments—vehicle, prazosin, and phenylephrine—over 10 minutes with sufficient washout between doses. The changes in blood pressure in response to each treatment were compared between the ambulatory oscillometric method and implantable telemetry in each animal. Blood pressure (BP) decreased after dosing with prazosin; increased, transiently, during dosing with phenylephrine; and did not change after dosing with vehicle.

INTRODUCTION

Having the capability to collect blood pressure from non-restrained animals is beneficial to reduce stress artifact associated with manual restraint (Gross and Luft, 2003). Additionally, remote collection of blood pressure reduces external stimuli placed on the animal from animal technicians. The current "gold standard" method for blood pressure collection for regulated cardiovascular preclinical studies (ICH S7A) of surgically implanted radiotelemetry is labor intensive to prepare and can increase the cost for acute studies for surgery and recovery procedures. Blood pressure collection in conjunction with a jacket may be the optimal design without physical restraint or surgical implantation of a telemetry device. There are conflicting statements in the literature about the accuracy and consistency of measurements of various non-invasive blood pressure collection devices, with some unable to meet validation standards (Bosiack, et al., 2010). Shih (2010) recently determined that the oscillometric device was not readily predictive of intra-arterial blood pressure during hypotension associated with acute hemorrhage in anesthetized dogs. Additionally, direct measurements of systolic, diastolic, and mean arterial blood pressures (SBP, DBP, and MABP) were underestimated by oscillometry and Doppler ultrasonic methods compared with telemetry with increasing differences in data sets during periods of hypertension (Haberman, et al., 2006; McMurphy, et al., 2006). Based on the variability documented in the literature for oscillometric blood pressure collection, the goal of this effort was to design a series of studies to challenge a newly designed oscillometric ambulatory method (emkaPACK) against direct measure of blood pressure via an indwelling arterial pressure catheter connected to a DSI telemetry device. Phenylephrine was chosen because of its known hypertensive properties as an α1-adrenergic receptor agonist and prazosin because of its known hypotensive effects as an α1-receptor blocker in vascular smooth muscle. Therefore, the purpose of this study was to assess, via telemetry, changes in blood pressure after intravenous infusion of phenylephrine and prazosin and evaluate the functionality of a commercially available non-invasive jacketed telemetry (emkaPACK) for the collection of blood pressure in dogs.

METHODS

This study was conducted after approval from the Institutional Animal Care and Use Committee of Battelle and in compliance with USDA regulations. A total of four Beagle dogs (two male and two female) were surgically prepared with implanted Data Sciences International radiotelemetry transmitter (D70-PCT), which has systemic arterial blood pressure and ECG data collection capabilities. Each animal's home cage was equipped with a Data Sciences International telemetry receiver and emkaPACK telemetry transmitters, receivers, and antenna. All four animals were also surgically implanted with vascular access ports in the jugular vein to allow for remote dosing with CADD plus infusion pumps. The dogs were conditioned to the undershirt and non-invasive telemetry jacket with pediatric tail cuff for 4 days prior to the day of dosing. The dogs were fasted overnight prior to dosing. On each day of dosing, the emkaPACK and CADD plus infusion pump were connected and placed in the jacket. A right-angle Huber infusion needle was placed into the vascular access port with appropriate sterile technique and connected to the CADD plus infusion pump. The tail was shaved approximately 6–8 inches from the base and wrapped with rolled gauze in order to secure the tail cuff (Figure 1). Following approximately 2 hours of baseline data acquisition, the dogs were infused with either 10 µg/kg/min phenylephrine, 40 µg/kg/min prazosin, or sterile water for injection (volume similar to test articles) over 10 minutes. Dosing was set to start 10 minutes after programming of the CADD plus infusion pump to allow for acclimation to the testing environment. After sufficient washout, the test articles were re-administered in a cross-over design to allow all animals to receive all treatments.

Figure 1. Illustration of the Positioning of the Tail Cuff and emkaPack to the Jacketed System on a Representative "Fake" Dog of Similar Size and Weight

RESULTS

Statistical Analysis: Blood pressure results for this study were reported as a combined mean (with standard errors) for both sexes. Analysis of variance (ANOVA) with repeated measures model was fitted separately to the baseline-adjusted data for each parameter and procedure type using the MIXED procedure in the SAS® System. Within each fit of the model, t-tests were run in the ANOVA to determine those post-dosing time points of vehicle or test article that were significantly different from the respective vehicle or test article baseline averages at an overall 0.05 level.

Non-Invasive Blood Pressure (NIBP) Assessment: The cuff inflated quickly and then deflated at a constant rate, capturing the pressure pulses associated with blood pressure. The initial inflation maximum pressure was set prior to study based on expected maximum blood pressures. This process can be repeated every 3 minutes. A filter was then applied to the cuff pressure signal to remove the constant component, leaving only the pressure pulses for analysis. This analysis consisted of plotting cuff pressure to pulse amplitude. Software capabilities allowed for the user to refine the analysis based on quality of the curve, "fit" of cuff pressure to pulse amplitude. Additionally, filtered pressure was overlaid on ECG over time to ensure each pulse had a corresponding ECG waveform (Figures 3, 4, and 5).

Effects of Test Articles on Blood Pressure Collected by Implanted Telemetry: Blood pressure remained unchanged after dosing with vehicle (water for injection). There were significant increases ($p \leq 0.05$), as compared with baseline, in blood pressure (SBP, DBP, and MABP) 2 minutes after the start of infusion of phenylephrine, which remained elevated until 24 minutes after the start of dosing. There were significant decreases, as compared with baseline, in blood pressure (SBP, DBP, and MABP) after the start of infusion of prazosin, which remained depressed through 30 minutes after the start of infusion (Figure 2 and Table 1).

Comparison of Post-Dose Time Points From NIBP and Telemetry: Blood pressure, at specific post-dose time points for a representative animal in each treatment group, was compared for the NIBP non-invasive jacketed telemetry method and invasive telemetry (Table 2). Both systems correctly measured an increase and decrease after dosing with phenylephrine and prazosin, respectively. However, considering arterial pressure measured by an indwelling catheter (invasive) with the signal transmitted via telemetry as the gold standard, the emkaPACK NIBP telemetry values for mean blood pressure were slightly higher than the values observed from DSI after dosing with phenylephrine (vasoconstrictor) and prazosin (vasodilator). The body position of the dog during these time points was unknown, which would affect the pressure between the two readings.

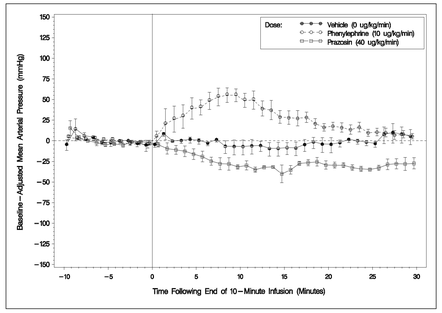

Figure 2. Mean Blood Pressure (mmHg) – Baseline-Adjusted Means (and Standard Errors) of Effects of Vehicle, Phenylephrine, or Prazosin in DSI Telemetered Beagle Dogs

Table 1. Mean Arterial Blood Pressure (mmHg) Means and Standard Errors of Unadjusted and Baseline-Adjusted Averages Following Dosing with Vehicle, Phenylephrine, or Prazosin

Time Following Dosing (minutes)	Unadjusted Averages			Baseline-Adjusted Averages		
	Vehicle (0 µg/kg)	Phenylephrine (10 µg/kg)	Prazosin (40 µg/kg)	Vehicle (0 µg/kg)	Phenylephrine (10 µg/kg)	Prazosin (40 µg/kg)
1	111.0 (13.4)	114.6 (4.7)	120.9 (9.6)	-5.3 (2.6)	5.0 (6.9)	-4.7 (2.7)
2	123.9 (13.5)	129.8 (9.4)	116.4 (10.2)	7.7 (2.3)	20.2 (18.9)*	-9.2 (6.7)
3	115.1 (12.1)	135.9 (7.5)	114.7 (11.6)	-1.2 (0.6)	26.3 (15.7)*	-10.9 (5.4)
4	115.6 (13.1)	139.2 (8.4)	113.0 (13.3)	-0.6 (2.5)	29.6 (14.2)*	-12.6 (6.5)
5	117.2 (14.2)	149.0 (7.6)	109.5 (12.0)	0.9 (3.6)	39.4 (12.9)*	-16.1 (6.6)
6	115.7 (13.8)	150.2 (6.0)	106.6 (12.9)	-0.5 (3.3)	40.6 (9.1)*	-19.0 (6.4)*
7	112.5 (9.9)	158.0 (5.2)	101.0 (12.8)	-3.7 (2.3)	48.4 (10.4)*	-24.6 (5.0)*
8	116.8 (12.3)	162.9 (4.1)	97.9 (15.3)	0.5 (1.9)	53.3 (10.8)*	-27.7 (7.2)*
9	108.6 (15.2)	164.9 (4.6)	97.7 (15.5)	-7.6 (7.8)	55.4 (8.8)*	-27.9 (7.5)*
10	108.4 (16.4)	164.9 (5.0)	94.0 (10.9)	-7.9 (9.1)	55.3 (7.7)*	-31.6 (2.6)*
11	108.3 (15.9)	158.7 (7.4)	95.9 (13.7)	-8.0 (9.0)	49.1 (8.5)*	-29.7 (5.5)*
12	109.2 (15.0)	159.0 (7.4)	90.6 (10.3)	-7.1 (8.8)	49.4 (11.0)*	-35.0 (3.2)*
13	109.5 (11.9)	148.8 (7.2)	93.5 (10.0)	-6.7 (6.1)	39.3 (9.1)*	-32.1 (2.0)*
14	105.9 (13.5)	147.0 (7.2)	94.1 (9.9)	-10.3 (8.3)	37.4 (11.7)*	-31.6 (1.6)*
15	106.1 (13.9)	138.7 (7.9)	85.7 (6.0)	-10.2 (8.4)	29.1 (7.7)*	-39.9 (10.8)*
16	107.0 (12.8)	137.8 (7.7)	90.4 (5.1)	-9.3 (7.2)	28.2 (8.1)*	-35.2 (5.2)*
17	106.5 (12.6)	137.1 (8.7)	98.4 (10.1)	-9.7 (8.3)	27.5 (9.3)*	-27.2 (2.3)*
18	110.7 (9.1)	138.2 (7.0)	99.3 (11.5)	-5.6 (7.2)	28.6 (6.2)*	-26.3 (3.6)*
19	113.8 (8.7)	130.5 (8.4)	100.2 (13.0)	-2.5 (6.8)	20.9 (6.1)*	-25.4 (5.2)*
20	111.2 (10.6)	126.0 (8.3)	96.3 (13.1)	-5.0 (8.9)	16.4 (4.7)*	-29.3 (5.1)*
21	111.0 (10.1)	127.5 (9.1)	96.2 (11.1)	-5.2 (9.3)	18.0 (4.7)*	-29.5 (3.6)*
22	113.0 (8.6)	125.9 (7.5)	96.2 (10.4)	-3.3 (4.3)	16.2 (5.7)*	-29.4 (3.0)*
23	116.9 (10.2)	123.4 (8.0)	93.1 (11.3)	0.7 (2.7)	13.8 (5.8)	-32.5 (3.4)*
24	115.3 (9.9)	126.3 (6.3)	91.7 (11.4)	-1.0 (3.0)	16.7 (5.9)*	-33.9 (3.1)*
25	113.7 (9.2)	119.5 (7.9)	90.8 (9.1)	-2.6 (3.2)	9.9 (4.2)	-34.8 (1.7)*
26	112.0 (9.6)	120.3 (7.6)	93.0 (9.3)	-4.3 (3.4)	10.7 (4.5)	-32.6 (3.2)*
27	123.0 (13.4)	119.6 (6.0)	97.2 (10.7)	6.7 (10.1)	10.0 (5.3)	-28.5 (6.5)*
28	125.3 (15.0)	116.6 (6.2)	97.9 (10.1)	9.0 (11.8)	7.1 (5.3)	-27.7 (6.2)*
29	123.4 (13.4)	117.7 (7.6)	97.6 (10.2)	7.1 (9.9)	8.1 (4.4)	-28.0 (7.9)*
30	120.7 (12.9)	115.3 (8.8)	98.4 (9.7)	4.5 (9.2)	5.7 (3.3)	-27.3 (6.7)*

Table 2. Initial Functionality Testing of Jacketed Unit: Blood Pressure Values From Tail Cuff Oscillometric Method and Telemetry at Specific Post-Dose Time Points

Blood Pressure Collection Method	Animal Number	Treatment	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Mean Arterial Blood Pressure (mmHg)
DSI Telemetry	1	Vehicle	137	100	112
	2	Phenylephrine	174	140	150
	3	Prazosin	114	62	80
emkaPACK Tail Cuff	1	Vehicle	147	103	127
	2	Phenylephrine	212	168	191
	3	Prazosin	96	70	84

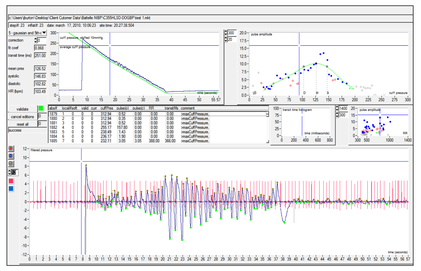

Figure 3. NIBP Telemetry – EMKA Screenshot of Cuff Pressure (upper left), a Plot of Cuff Pressure Plotted Against Pulse Amplitude (upper right), and Filtered Pressure With ECG Overlay for a Single Animal Treated With Vehicle

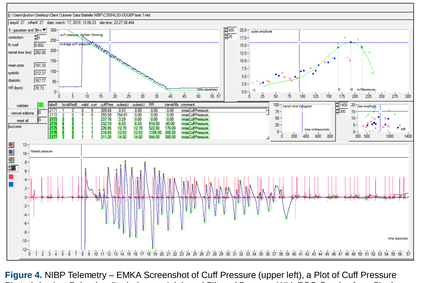

Figure 4. NIBP Telemetry – EMKA Screenshot of Cuff Pressure (upper left), a Plot of Cuff Pressure Plotted Against Pulse Amplitude (upper right), and Filtered Pressure With ECG Overlay for a Single Animal Treated With Phenylephrine

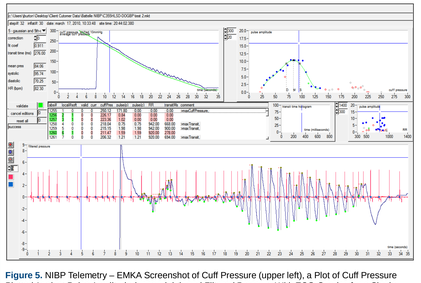

Figure 5. NIBP Telemetry – EMKA Screenshot of Cuff Pressure (upper left), a Plot of Cuff Pressure Plotted Against Pulse Amplitude (upper right), and Filtered Pressure With ECG Overlay for a Single Animal Treated With Prazosin

DISCUSSION

To determine whether the test articles were appropriate to meet the objectives of the study, the appropriate doses and route of administration needed to be determined. A vital component in studying blood pressure altering drugs is having a test system where the cardiovascular system is stable and at resting conditions. Additionally, administering the test articles intravenously would allow for an immediate response. Therefore, a subcutaneous vascular access port was placed in the jugular vein of each animal for intravenous access via an ambulatory infusion pump. Dosing the animals remotely allowed heart rate and blood pressure to stabilize to resting levels prior to dosing, an optimal situation for telemetry assessment of the cardiovascular system. The use of the ambulatory infusion pumps also allowed for increasing the dosing time to 10 minutes as opposed to a bolus injection, maximizing the vasoactive effects of the test articles for a longer period of time. The changes in blood pressure in response to the two test articles were significant, reassuring that sensitivity and specificity of the model were met.

The tail cuff method of blood pressure collection has a current minimum repeat time of 3 minutes, and this allowed for at least three cycles to occur during the infusion of phenylephrine (very short half life). The maximum and minimum cuff pressure during inflation and deflation, respectively, were appropriate for the collection of pressure for these vasoactive drugs, which are user defined. The placement of the tail cuff was determined to be the critical aspect of blood pressure collection, and proper position was assured by identification marks on the tail cuff. Anchoring the tail cuff in position is dependent upon the length of the inflation/deflation tubing (Figure 1).

The measurement of systemic blood pressure is dependent upon the location within the arterial tree where the pressure is measured. Systolic pressure progressively increases in magnitude at increased distances from the heart. Further, the magnitude of the pressure observed will differ with orientation of a pressure catheter within the vessel being measured. A relatively higher pressure will be recorded when a catheter is placed into the flow of blood as opposed to at right angles to the flow. The elevation (or depression) of the pressure sensor relative to the vessel being measured will also alter the pressure recorded. For example in a dog, the telemetry pressure catheter is frequently placed with its tip in a major vessel above the sensor (located in the transmitter) placed in the abdomen. In a standing dog, this arrangement results in a modest increase in measured pressure as compared with the pressure where the tip of the catheter is located.

In contrast, pressures measured via a cuff device typically employ an inflatable cuff placed around the tail of the dog. The cuff width must be matched to the circumference of the tail to obtain accurate measurement. The oscillometric method is commonly employed in most automated blood pressure devices. For this method, the pressures within the cuff provide the systemic pressure measures. Pressure within the cuff is slowly decreased. Systolic pressure is determined at the initiation of oscillation in the cuff. The cuff pressure at which maximum pulsations are observed while the cuff is deflating is mean arterial pressure. Diastolic pressure values are calculated.

These inherent differences between the two different methods of pressure measurement suggest that to observe somewhat different pressure values should be anticipated. However, the differences between the two measurement techniques were small; further and more important, the pressures measured during the chemically induced alterations were consistent between the two techniques.

CONCLUSION

The doses of each test article used in this study created a response that was sufficient in magnitude and duration to allow for comparisons to be made between the two telemetry systems. The NIBP telemetry system was able to detect increases and decreases in blood pressure at specific post-dose time points. Additionally, there did not appear to be any effect (cardiovascular or behavioral) on the dog as measurements were continually collected by the NIBP system. Based on these initial findings of this study, additional experiments will be scheduled to assess the NIBP method of blood pressure collection in canines dosed with blood pressure-altering drugs. Specifically, the goal of these experiments will be to determine if sufficient post-dose blood pressure samples can be collected by the NIBP telemetry system, consistently, through 24-hours post-dose.

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