Inclusion of Blood Pressure Measurements in Canine Toxicology Studies

Validation of a non-invasive telemetry method

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Introduction

The current gold standard for cardiovascular safety evaluation of new drugs in safety pharmacology studies in large animals is the use of invasive implanted transmitters. However these studies are generally designed to evaluate acute effects of compounds so a method of evaluating repeated dosing over longer periods of time is needed. While the use of non-invasive external telemetry is becoming a new standard for ECG recordings, simple options for blood pressure assessment are still to be defined.

Current Method

Currently, the method used to measure blood pressure in our sub-chronic and chronic toxicology studies is an invasive ear catheter. This method has many disadvantages, firstly it is invasive and the animals have to be restrained in order for the catheter to be inserted. This process is stressful for the animals which may affect the quality and accuracy of the data recorded. Also using this method you can only get a snap shot result of about 30 seconds and it can only be repeated twice a day, once a week due to recovery of the ear artery.

NIBP System

Recent advances in technology have led to a new way of measuring non-invasive blood pressure using high-definition oscillometry.

What is it? The blood pressure device designed by EMKA technologies uses indirect oscillometric tail cuff measurements and the well-established principle of blood flow occlusion of the medial coccygeal artery to measure blood pressure in the freely moving dog.

How does it work? The dogs are equipped with surface ECG electrodes and a jacket which is used to carry the external telemetry equipment. A blood pressure cuff as seen in the picture below is placed around the base of the tail (shaved beforehand to ensure better contact with the artery) and left for the duration of recording (up to 24hrs). The signal is picked up by an aerial in the pen and the data is automatically uploaded onto the computer.

Advantages	Disadvantages
This system is non-invasive reducing the stress to the animal.	However due to the nature of the jackets and tail cuffs the dogs require training so they become accustomed to wearing the jacket and cuffs.
The packs used in this new system are quiet and only take 40s-1min to perform a cycle (a cycle being one inflation and deflation).	No continuous trace available limiting correlation with ECG findings.
Blood pressure recordings up to 24 hours which gives a better idea of any effects the compound may be having over time	
ECG and respiratory parameters can be added on and recorded simultaneously.	

Results

Figure 1 shows a raw blood pressure trace for one cycle of tail cuff inflation/deflation vs. time. The blue line is the original trace where each individual spike is a blood pressure pulse and the green line shows the baseline filter. Figure 2 shows a plot of pulse pressure vs. time obtained by subtracting the green line from the blue line in figure 1 (which removes the background cuff pressure). The pulse pressure plot in figure 2 is processed using an EMKA proprietary detection algorithm which validates each individual pulse dependent on a number of criteria (which we are validating). Valid pressure pulses produce an XY plot of pulse amplitude versus average cuff pressure (Figure 3). A curve is fitted through the valid pulse points and is plotted in green allowing values for systolic and diastolic pressure to be extracted.

Figure 1. Raw blood pressure signal (cuff pressure vs. time)

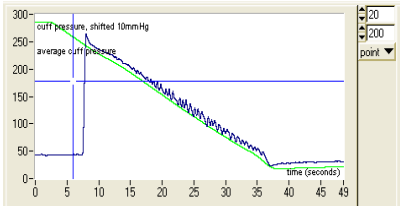


Figure 3. Processed blood pressure signal

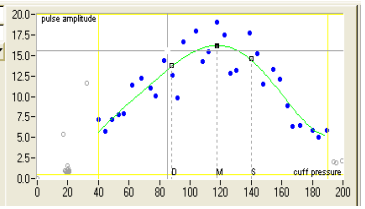


Figure 2. Plot of pulse pressure vs. time

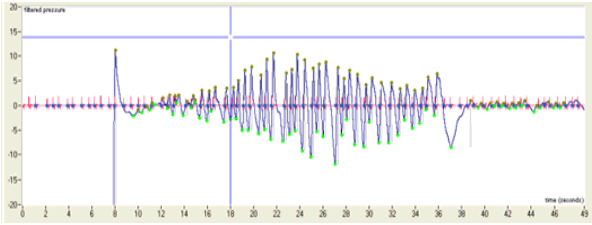
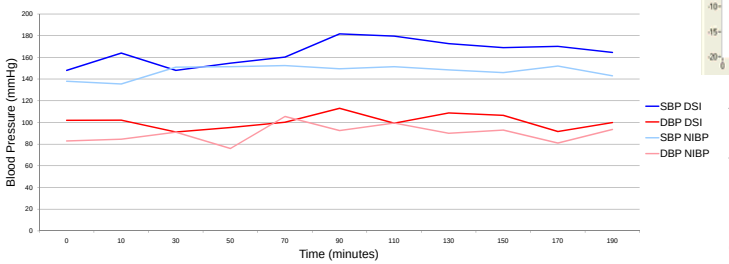


Figure 4: Correlation between results obtained from the NIBP system compared to the implanted DSI catheter (mean values from 2 dogs).



As seen in figure 4 there are small differences in blood pressure values recorded with the NIBP system compared to the invasive catheter. Overall the values for both SBP and DBP are lower with the NIBP system than the DSI catheter. This difference can be explained by the fact the NIBP system measures pressure in the medial coccygeal artery, where as the implanted catheter measures pressure directly in the descending aorta.

Study Validation Plans

To begin with we have already assessed the acceptance of the jacket and cuff, characterised the length and duration required to jacket train and determined the optimal positioning of the cuff along the tail artery.

The second phase of the study validation will investigate the number and frequency of tail cuff inflations required to get a successful and accurate blood pressure measurement, and comparing baseline signal with the DSI implanted telemetry system.

The third phase will involve a cross validation of the EMKA non-invasive blood pressure system with the DSI implanted system to detect changes in blood pressure in response to reference compounds known to cause hypertension or hypotension.

Future Work

Once validated the NIBP system will be incorporated into toxicology studies as an add-on to the current 24 hour ECG recordings. As an extension to this study non-invasive respiratory assessment in conscious free-moving dogs using EMKA respiration belts will be investigated. Safety pharmacology respiratory evaluations are, in most cases, stand-alone studies in rodents (Hoymann, 2007), while the assessment of effects on the cardiovascular function is investigated in large animals. The idea of combining cardiovascular (CV) and respiratory evaluation on the same study is very attractive; it will allow us to investigate the cross-over between the different body systems in response to various compounds and may help the reduction of animal use and study cost.

References H.G. Hoymann, Invasive and noninvasive lung function measurements in rodents, *Journal of Pharmacological and Toxicological Methods* **55** (1) (2007), pp. 16–26.

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