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Original article

# Evaluation of blood flow parameters in addition to blood pressure and electrocardiogram in the conscious telemetered beagle dog

Gemma L. Taylor *, Bela Patel, Andrew T. Sullivan

*Safety Pharmacology, GlaxoSmithKline, The Frythe, Welwyn, Herts, AL6 9AR, UK*

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**Abstract**

**Introduction:** The objective of this study was to evaluate a model for measuring blood flow parameters in addition to blood pressure, heart rate and electrocardiogram (ECG) in conscious telemetered restrained and unrestrained beagle dogs. **Methods:** Male beagle dogs were instrumented with fully implantable ITS radio telemetry devices for the measurement of blood pressure and ECG. In addition, the dogs were instrumented with a probe around the pulmonary artery for the measurement of blood flow by ultrasound. Dobutamine at 5, 10 and 20 μg/kg/min, given intravenously to sling restrained animals ($n=4$), and minoxidil at 2 mg/kg, given orally to unrestrained animals ($n=4$), were selected as test compounds known to cause changes in the cardiovascular parameters of interest in this work. **Results:** Dobutamine produced a small increase in mean (9%) and systolic blood pressure (5%), and an increase in pulse pressure (37%) and heart rate (30%). The additional blood flow parameters showed that dobutamine also increased stroke volume (21%) and cardiac output (58%) and reduced total peripheral resistance (52%). Minoxidil treatment resulted in a prolonged reduction in mean, systolic and diastolic blood pressure (up to 24%). Additionally, a prolonged increase in heart rate (169%) and cardiac output (120%) were observed along with a reduction in total peripheral resistance (62%). The effects of both compounds were consistent with their known pharmacology. **Discussion:** The results show that measurement of blood flow parameters can be successfully added to the standard telemetered cardiovascular dog model to provide valuable additional information on the effects of compounds on the cardiovascular system.


*Keywords:* Beagle dog; Blood flow; Cardiac output; Dobutamine; Methods; Minoxidil; Stroke volume; Telemetry; Total peripheral resistance

## 1. Introduction

The preferred model for cardiovascular safety pharmacology studies described in the ICH S7A guideline is the conscious dog, with the measurement of blood pressure, heart rate and ECG by telemetry being the gold standard approach (ICH S7A, 2000). However, the shift from anaesthetised models and the increased use of telemetry has reduced the number of parameters available for measurement, and parameters such as blood flow are no longer routinely included. The aim of this study is to investigate the feasibility of measurement of blood flow parameters in addition to blood pressure and ECG in the conscious restrained and unrestrained telemetered dog.

Mean blood pressure is the product of cardiac output and systemic vascular resistance (Guyton, 1981). Either an increase in cardiac output or an increase in peripheral resistance will result in increased mean arterial pressure. However, if both parameters were to change equally but in opposite directions then mean blood pressure would not change. Thus, although a change in mean arterial pressure in a safety pharmacology study is a clear indication that a test compound has an effect on the cardiovascular system, the absence of a change in mean arterial pressure does not necessarily mean that a compound is without cardiovascular effects.

The ability to capture pulmonary arterial blood flow signals enables the measurement of additional parameters such as cardiac output and the calculation of stroke volume and total peripheral resistance. Cardiac output is the volume of blood pumped out by the heart in 1 minute, and stroke volume is the volume of blood ejected by the heart in one beat; it is calculated as the cardiac output divided by heart rate. Total peripheral resistance, calculated from mean blood pressure divided by cardiac output gives a measure of the tone of the vasculature of the circulatory system (Guyton, 1981).

* Corresponding author. Tel.: +44 1438 782401; fax: +44 1438 782582.
*E-mail address:* Gemma.L.Taylor@gsk.com (G.L. Taylor).

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Dobutamine and minoxidil were selected as test compounds known to cause changes in the blood flow parameters being evaluated in this work. Dobutamine is a $\beta_1$-adrenergic receptor agonist and has a positive inotropic action, thereby increasing the force of contraction of the heart. At doses between 2 and 42.5 μg/kg/min dobutamine is reported to increase cardiac output, stroke volume, heart rate and blood pressure and decrease total peripheral resistance in conscious dogs (Hettrick, Pagel, Lowe, Tessmer & Warltier, 1996; McEntee et al., 1998; Sato et al., 1997; Vatner, McRitchie, & Braunwald, 1974). To produce a dose related response intravenous doses of 5, 10 and 20 μg/kg/min were selected for this study. Minoxidil is a potent vasodilator and relaxes vascular smooth muscle by selectively increasing membrane permeability to potassium ions. An oral gavage dose of minoxidil at 2 mg/kg was chosen for this study, at this dose minoxidil was expected to increase cardiac output and heart rate and decrease blood pressure and total peripheral resistance in conscious dogs (Hanton, Gautier, & Bonnet, 2004; Humphrey & Zins, 1984).

## 2. Methods

All animal work described in this paper was carried out under the authority of a UK Home Office licence, and was approved by internal ethical review processes.

### 2.1. Surgical implantation

Male beagle dogs ($n=6$) supplied by B&K Universal UK, approximately 9 to 12 months of age, were instrumented with fully implantable ITS radio telemetry transmitters (T27F, RMISS, Inc, USA, Fig. 1) for the measurement of aortic blood pressure (BP) and chest electrodes approximating to a Lead II ECG signal. In addition, the dogs were instrumented with a flow probe (Triton Technology, Inc, Fig. 1) around the pulmonary artery for the measurement of blood flow (BF). Prior to surgical implantation, the blood pressure transducer of the T27F implant was calibrated and both the implant and the flow probe were sterilized using a low pressure ethylene oxide process. Animals were pre-medicated with Acepromazine (0.03 mg/kg of 2 mg/mL solution) and Pethidine, i.m. (3 mg/kg of 50 mg/mL solution) prior to induction of general anaesthesia with Rapinovet (propofol, 4 mg/kg of 10 mg/mL solution, i.v.) to effect and maintenance using isoflurane (2–2.5%) in nitrous oxide and oxygen. All surgical procedures were carried out under aseptic conditions using sterilized equipment.

The dogs were placed in the lateral recumbency position and a left thoracotomy was performed between the fifth and sixth intercostal space. A small incision was made in the abdominal wall, sufficient to house the main body of the telemetry implant. The cable with the pressure transducer and ECG leads was then fed through to the chest area via a small hole in the diaphragm. The battery and transmitter units were placed in between the muscle layers in the abdomen along either side of the midline incision. The switch component of the implant was placed in a subcutaneous pocket in the abdominal region and the antenna guided subcutaneously to run parallel to the spine. The abdominal incisions were then closed.

For implantation of the flow probe, the ribs were spread and lungs retracted to one side, the phrenic nerve carefully dissected and secured to one side for protection during the procedure. The skin button of the flow probe was guided subcutaneously from the thorax and exteriorised through the skin at the back of the neck. The pericardium was cut to expose the heart and the C shaped cuff (Fig. 1) of the flow probe was placed around the pulmonary artery following careful removal of all surrounding fat tissue. The blood pressure transducer (which also serves as one ECG electrode) of the T27F implant was implanted next. Following a dissection around the thoracic aorta, just below the aortic arch, a purse-string suture was positioned where the transducer was to be placed and the vessel clamped to stop blood flow. The pressure transducer was inserted into the aorta, sutured into place and blood flow was then restored. To close the chest the rib retractor was removed and a nerve blocking agent, Marcain (bupivicane hydrochloride 0.5%, 10 mL), injected into the ribs and surrounding muscles. The phrenic nerve and lungs repositioned and the second ECG electrode was placed subcutaneously at the level of the 6th intercostal space, the chest was then sutured closed, the pneumothorax evacuated and spontaneous respiration re-established.

Recovery from surgery was aided with morphine immediately post-op and with buprenorphine induced analgesia and carprofen antibiotics, administered in the days following surgery as required. Dogs were then allowed to recover, with reduced exercise and single housing, for at least 4 weeks before use on studies. The implantation of all six flow probes was successful and each flow probe remained functional for between 6 and 12 months.

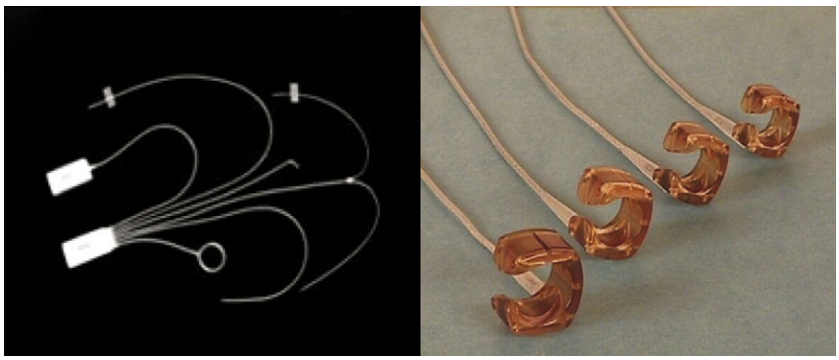

Fig. 1. Fully implantable ITS radio telemetry implant (T27F, RMISS, Inc, USA) and flow probes (Triton Technology, Inc).