Telemetry in the Minipig:

Is the non-invasive, jacketed monitoring approach an alternative to the implantable model?

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Implantable telemetry

The preferred model for performing safety pharmacology studies on the cardiovascular system according to the ICH S7A is the conscious animal monitored under unstressed, physiological conditions. A typical cardiovascular safety pharmacology study of a conscious non-rodent usually includes the measurement of systemic arterial hemodynamic and electrocardiogram (ECG). Implantable telemetry technology is considered the "gold standard" approach for monitoring hemodynamic parameters such as heart rate, arterial blood pressure and ECG of unrestrained, freely moving animals, given that it allows data to be collected continuously in conditions of reduced stress. Full-implant telemetry systems usually permit the measurement of arterial blood pressure and a single lead (Lead II) electrocardiogram. Under certain conditions, ventricular blood pressure measurement (and left ventricular contraction index) or multiple ECG leads recording can also be envisaged. Implantation of telemetry devices requires invasive surgery and post-operative care. More recently, an external telemetry solution was introduced for collecting ECGs in non-rodents. This technology is gaining interest and acceptance as another tool for generating cardiac drug-safety data, especially in regulatory toxicology studies.

The dog is the non-rodent species most commonly used in safety pharmacology telemetry studies; the primate is usually considered when the dog has been shown to be inappropriate.

In 2005, the Japanese QT PRODACT programme evaluated the telemetered NIBS minipig for assessing drug-induced cardiovascular effects and QT interval prolongation in safety pharmacology studies, testing haloperidol, propranolol and dl-sotalol as reference cardiovascular compounds. This study concluded that the telemetered minipig is a suitable non-rodent model for assessing drug-induced QT-interval prolongation. The preliminary effort to validate the minipig for pharmacological testing was more recently completed with an in-depth cardiovascular evaluation performed by the Boehringer Ingelheim General Pharmacology Group (Germany), using the telemetered Göttingen Minipig. Hemodynamic (heart rate, aortic pressure, left ventricular pressure, left ventricular *dP/dt* max.) and electrocardiographic (PR, QRS, QT, RR) parameters were evaluated, as well as body temperature in a cohort of seven freely moving Göttingen minipigs monitored over 24 hours. Diurnal effects were analysed and the dependency of the QT interval duration versus heart rate was also addressed. In that model, moxifloxacin (a third-generation synthetic fluoroquinolone known to prolong QT interval duration) showed the expected dose-dependent effects on the QT-interval, when orally administered at doses leading to clinically relevant plasma drug concentrations. On the other hand, propranolol demonstrated the expected prototypical effect of a beta-adrenoceptor blocking agent with anticipated effects on heart rate and myocardial contractility.

That pharmacological validation work was complemented by the data presented at the Safety Pharmacology Society meeting in 2008 (Madison, USA) by the Minipig European Consortium Project,[1] including pharmacological cardiovascular effects of dofetilide (class III anti-arrhythmic agent, known to prolong QT interval duration) and pimozide (antipsychotic drug with long QT syndrome side effects).

With this body of publications, the telemetered, freely moving minipig model is entering a new era, and should now be considered a suitable model for non-rodent cardiovascular safety pharmacology studies. These publications have provided a solid methodological approach and produced a convincing and significant amount of pharmacological data.

External telemetry

An increasingly popular trend, particularly encouraged by several regulatory guidelines (ICH S7A; ICH S6, ICH M3(R2); ICH S9) is the incorporation of safety pharmacology, and particularly cardiovascular, end-points into toxicological studies. This is an interesting concept in that it leads to a better integration and understanding of the relationship between the pharmacological properties and the toxicity liability of an NCE as well as a reduction in the number of animals tested.

In regulatory toxicological studies, ECG and blood pressure are typically collected under chemical or physical restraint. This approach entails a number of drawbacks, such as the sedation and/or the anaesthesia, which could be possible confounding factors; the cardiovascular stress induced by the handling of the animals; and the limited data collection imposed by the restraint conditions.

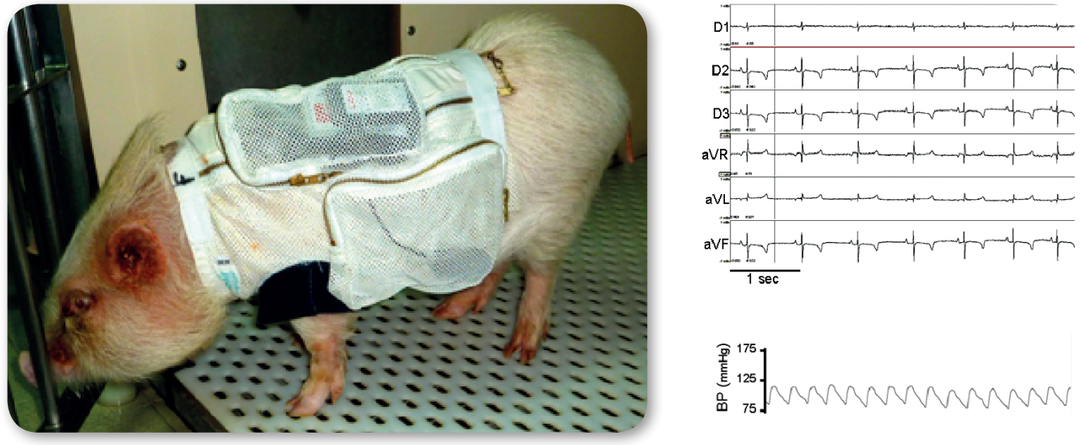
A variety of non-invasive jacketed telemetry systems for use in freely moving animals are now available. This technology offers the possibility to non-invasively record and analyse the ECG and blood pressure in a detailed, temporal manner and is a more satisfying approach than the methodology traditionally adopted in regulatory toxicology studies. Some of the vendors currently manufacturing external telemetry devices are also proposing the possibility of assessing the respiratory function. This consists of measuring changes in respiratory volume by evaluating changes in the electrical characteristics of a set of bands around both the chest and abdomen (respiratory inductive plethysmography, RIP).

In preparing for a non-invasive jacketed telemetry study, animals are usually acclimatised to the externally-worn wireless telemetry device (jacket) and shaved at locations where ECG skin electrodes are to be placed. An undergarment is generally positioned underneath the jacket to secure the skin electrodes/RIP bands and to prevent the animal from accessing the leads.

At Ricerca Biosciences, Lyon, the external telemetry approach is currently used in dog, monkey and minipig toxicology studies, both short and long-term in duration.

We have generated data demonstrating that jackets were sufficiently sensitive to detect heart-rate and QT changes following different cardiovascular modifying drugs that were comparable to those derived from implants. As such, this method is an invaluable tool for obtaining high-quality ECG data from toxicology studies.

At Ricerca Biosciences, Lyon, we also believe that the Minipig is going to play a role in the preclinical cardiovascular risk assessment in modern drug development. The placid temper of the minipig and the constitution of its skin, which enables an excellent contact with the surface electrodes, represent undeniable advantages for successfully utilising jacketed external telemetry in this animal species.



A Göttingen minipig equipped with an external jacketed telemetry system (JET™ Blood Pressure; Data Science International, St Paul, USA). This non-invasive jacketed telemetry allows continuous monitoring of a six-lead ECG (right upper panel) and blood pressure (right lower panel). The JET™ Blood Pressure add-on module consists of a remote antenna receiver and electronics module that are interfaced directly to the JETÔ device. Together these components receive a signal from a pressure implant placed in the femoral artery to enable direct blood pressure measurement via a simple, fast, and minimally invasive surgical procedure.

[1] In 2006, (initially encouraged by H. Lundbeck A/S), a consortium gathering several pharmaceutical companies and contract laboratories all based in Europe was formed to perform a characterization of the minipig in cardiovascular safety pharmacology, a collaboration which includes *in vitro* and *in vivo* assessment. The objective of the *in vivo* investigations is to test several drugs considered as reference cardiovascular compounds. Designated compounds were assigned to the different participant sites, and the QT-prolonging drug Dofetilide was tested by all sites and used as an indicator of inter-site variability.