SIMULTANEOUS WIRELESS MEASUREMENT OF BLOOD PRESSURE AND SYMPATHETIC NERVE ACTIVITY

A System for Investigating Neural Control Mechanisms in Long Term Blood Pressure Regulation

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Abstract: We report on the development of a combined sympathetic nerve activity and blood pressure telemeter for long term implantation in freely moving small animals. The devices simultaneously records and transmits blood pressure, temperature and sympathetic nerve data on the 2.4 GHz ISM band with a range of 5 m. Blood pressure is measured with a 400 Hz bandwidth, fluid filled catheter at a resolution of 0.1 mmHg. Sympathetic nerve activity is measured differentially using stainless steel electrodes attached to the renal nerve. The telemeter measures 29x37x12mm (a volume of approximately 9.5 cm^3) and weighs 17g, making it suitable for use in rats with a weight greater than 170 g. Battery life is 12 h when used continuously, however the device's lifespan is effectively indefinite due to the use of in vivo inductively coupled battery charging. Example data recorded in a conscious unconstrained rat is provided which verifies the telemeters operation.

1 INTRODUCTION

Elevated blood pressure is a well established factor in determining an individual's risk of developing a number of serious diseases, including heart failure, renal failure and stroke (Whelton and Klag 1989; MacMahon 2000). Although the short-term regulation of blood pressure is well understood, not much is known about the regulation of blood pressure over the longer-term.

Recently, with the development of long life implantable telemetry, researchers have been able to investigate the role of the sympathetic nervous system in regulating blood pressure over longer time periods and under more natural unconstrained conditions. It is clear that the sympathetic nervous system is key to the short term regulation of blood pressure. However, much less is known about its role in regulating blood pressure over long time periods (Mark 1996). One method of investigating this relationship is to measure the sympathetic nervous system's output directly by exposing nerve fibre bundles and recording action potentials directly. The level of sympathetic nerve activity

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(SNA) can then be compared with simultaineoulsy aquired blood pressure measurements; allowing researchers to experimentally investigate their interaction.

Previously, researchers have had to implant two seperate devices in order to record blood pressure (Data Sciences International,St Paul, Minnisota) and SNA (Telemetry Research, Auckland, New Zealand) simutaineously over long periods of time (Barrett, Ramchandra et al. 2003). This has meant that research has typically been constrained to larger animals such as rabbits. In this paper we present a combined SNA and blood presssure telemeter that can be implanted in animals as small as rats.

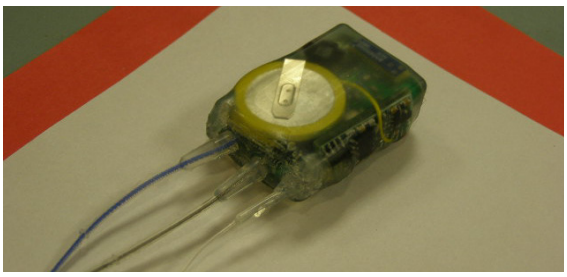

Figure 1: The SNA and BP telemeter.

Figure 2: Wireless charger (right rear) and charging pad (foreground), implantable telemeter (on charger pad), and analogue reconstruction units for pressure and SNA (left rear).

Figure 1 shows the new experimental telemeter. The leftmost leads are the nerve electrodes. At the right is the fluid filled catheter for BP measurements. Visible on top is the rechargable lithium ion coin cell which provides power to the telemeter between chargings. Inductive power transfer is used to recharge the battery anytime while still implanted. The electronics and electrodes are incapsulated in medical grade silicon elastomer. The telemeter measures 25x37x12mm (W x L x H, excluding electrodes and catheter), occupies a volume of approximately 9.5 cm^3 and weighs 17g, making it suitable for use in rats with a weight greater than 170 g (Moran, Roy et al. 1998).

Table 1: A Comparison between two existing commercial telemeters which are capable of measuring both blood pressure and bio-potential signals (Data Sciences International C50-PXT and Konigsberg T31F) and the new type.

	C50-PXT	T31F	New
LxWxH	30x15[1]	33x15x10	29x37x10
Volume	6	5	9.5
Weight	11	13	17
#Bio Channels	1	2	1
Bio Bandwidth	1-100Hz[2]	0.1-250 Hz[2]	1-4 kHz
Pk-Pk Range	Unknown	1 mV[3]	120 µV
BP Bandwidth	<100Hz[4]	>1KHz	120Hz
Stability	5 mmHg	3 mmHg[2]	T.B.D.
Batt Life	2 month	6 month	12 hour[5]
#Trans Ch.	1	20	12
Trans. Type	AM	FM	2.4GHz

1. Cylinder (Length x Diameter).
2. Best estimate based on other devices made by the manufacturer.
3. Smallest available input range.
4. Measured using frequency response rig.
5. Between charging.

Table 1 presents a summary of the specifications of the new telemeter and its nearest comercially available equivalents. These comparison devices were chosen based on their size (small enough to be used in a rat) and ability to measure both biopoential signals and blood pressure. The major areas where the new device differs from its equivelents are the higher bandwith and sensitivity of the biopotential ampifier, the abiltiy to recharge the new divice in vivo and the use of a digital transmision system.

2 METHODS

2.1 System Architecture

The heart of the system is an 8051 microcontroller which acts as an interface between the various systems. An 8 channel (multiplexed) 12 bit A/D converter is used to digitise recorded data. A bi-directional transceiver operating on the 2.4 GHz ISM band is used for communication, including data transmission. This has a number of advantages including the ability to wirelessly schedule

measurements in vitro. Additionally, 12 channels are available for communication, allowing multiple instrumented animals to be housed in close proximity.

Power is provided wirelessly to the implant using inductively coupled power transfer (Budgett, Hu et al. 2007). This has allowed high power devices (relatively speaking) such as A/D converters, microcontrollers and digital transmission systems to be used. During use, the implant can be charged by placing a coil under the animal's home cage through which high frequency AC current is passed. Power is received at the implant by a ferrite pickup which is magnetically coupled to the charging coil. Information about the charge state of the battery and power received are embedded in the BP/SNA data packets and transmitted to the wireless power supply. The magnetic field can then be controlled such that only the required amount of power is delivered to the implant. This reduces the temperature rise during charging to approximately 5°C.

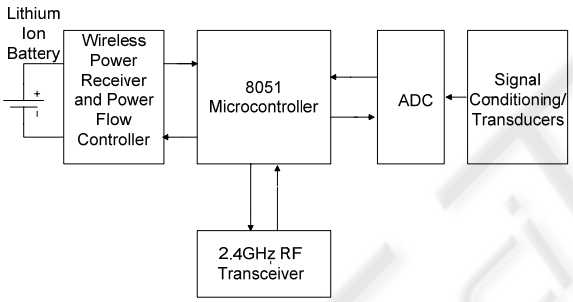

Figure 3: Block diagram of the telemeter.

Between charging, a 70 mAH lithium ion coin cell provides power. Consumption is 6 mA during continuous operation which results in a battery life of 12 h. In vivo charging takes between 2 and 4 hours and is dependent on how active the animal is and how close the implant's orientation is to the optimum for charging. During charging SNA recording is not possible as the nerve signal is swamped by noise generated by the 200 kHz charging field.

2.2 Blood Pressure Measurements

Blood pressure measurements are performed using a 10cm fluid filled polyurethane catheter, which acts as an interface between the measurement site (for instance the aorta) and the piezo resistive pressure transducer in the telemeter. Pressure waveforms are transmitted along the catheter using low viscosity biocompatible fluid. No obvious reference pressure is available internally to make measurements against. Therefore, an absolute pressure sensor (one with an internal vacuum reference) is used. Physiologically, the pressure of interest is the difference between the blood pressure and the ambient or atmospheric pressure. This pressure is derived by measuring the atmospheric pressure using a second absolute transducer and subtracting it from the internal pressure.

2.2.1 Frequency Response

Accurate measurements of systolic and diastolic pressure require the use of a wide bandwidth measurement system. One historical rule of thumb is that the bandwidth should be greater than 10 times the heart rate (Gabe 1972). For a rat, the maximum heart rate that can be reasonably expected is 500 beats per minute. This requires a bandwidth of greater than 80 Hz.

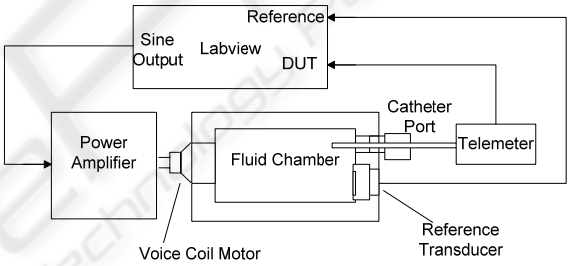

Figure 4: Frequency Response Measurement System.

In order to characterise the telemeters pressure measurement bandwidth, the rig represented by Figure 4 was constructed. A fluid filled chamber acts as a pressure source for frequency response measurements. Pressure waveforms are generated by a voice coil actuator which exerts force on the fluid through a thin brass diaphragm. The catheter of the device under test (DUT) is inserted into the chamber using a luer lock adaptor. A second high bandwidth transducer provides a reference pressure for calculations. Provided compliance of the chamber is minimized, the system's measurement bandwidth can be high. Bandwidths of 5 kHz (-3 dB) have been attained with usable signals present until approx 15 kHz.

Tests are preformed using the swept sine technique where sinusoidal perturbations are applied to the DUT. The LabVIEW Sound and Vibration Analysis Toolbox (www.labview.com) automatically calculates the magnitude transfer function from reference pressure (P_{ref}) to telemeter output (P_T) as defined by equation 1.

A typical transfer function is presented in Figure 5. The bandwidth (-3 dB point) of the catheter/amplifier combination (blue) is 400 Hz. This is more that four times greater than the required bandwidth of 80 Hz as described above. Gain peaking is evident at around 100 Hz, but its magnitude is exaggerated by the small vertical scale and only amounts to a 15% increase in gain. The small dip in magnitude at 50 Hz is due to power line interference (in the test rig).After sampling at 500 Hz, transmission, reconstruction and filtering the -3 dB frequency is reduced to 120Hz.

$$\left\|M(j\omega)\right\|_{dB} = 20Log\left\|\frac{P_T(j\omega)}{P_{ref}(j\omega)}\right\| \quad (1)$$

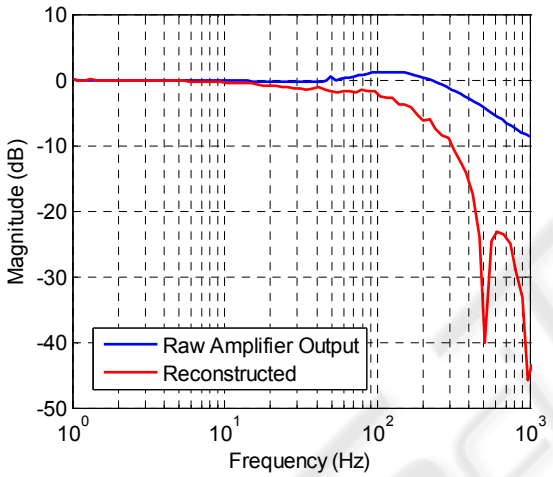

Figure 5: Frequency Response of the blood pressure measurement system. Amplified pressure sensor output (blue) and reconstructed response after transmission (red).

2.3 SNA

2.3.1 The Nature of SNA

Postganglionic sympathetic nerves are composed of multitudes of unmyelinated fibres. The action potentials generated by individual fibres are small and difficult to measure. Because of this, the entire nerve bundle is usually used when recording SNA. Typically two electrodes placed on the nerve and a differential measurement is made. Measurable voltages result as large numbers of fibres fire almost simultaneously whose contributions are additive in nature. Even so, the potentials generated by a whole bundle are still only in the µV range. This, combined with the relatively high frequency content of the signals (into the kHz range (Malpas 1998)) make instrumentation troublesome, and especially so in a micro power telemetry system.

2.3.2 Signal Acquisition

Figure 6 shows the approach taken, which is similar in nature to many previously described AC coupled bio-potential amplifiers (Prutchi and Norris 2005).

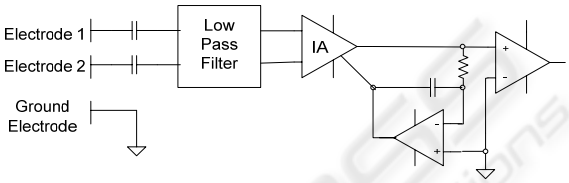

Figure 6: Nerve Electrode Amplifier.

With a system gain of 10000 and a 3V power supply, the amplifier is susceptible to saturation due to electrode polarization offsets. Capacitively coupling the active electrodes reduces the likely hood of this happening but requires the use of a third reference electrode. A low noise Instrumentation amplifier (IA) amplifies and level shifts the signal for analogue to digital conversion. A servo amplifier monitors the DC level of the nerve signal and centres it in the A/D converter's range. This is effectively a second form of AC coupling but also improves headroom by reducing the effects of input offset voltage. With a gain of 10000, the typical input offset voltage of an instrumentation amplifier (50 - 500 µV) could easily cause saturation. Digitization is performed using a 12 bit A/D running at 8 kHz. Full scale input range is ±60 µV. Intrinsic noise is 650 nV_{RMS} over the devices Bandwidth of 1 Hz-4 kHz. This results in a signal to noise ratio of 37 dB for a full scale sinusoidal input.

3 EXPERIMENTAL RESULTS

3.1 Experimental Procedure

Experiments were conducted in Wistar rats with initial minimum weight of 250g and were approved by the University of Auckland Animal Ethics Committee (approval R543). The rats were housed individually in standard rat cages, with food and water available ad libitum. The room was kept at a constant temperature (18 °C) and dark-light cycle (lights on from 0600 to 1800).

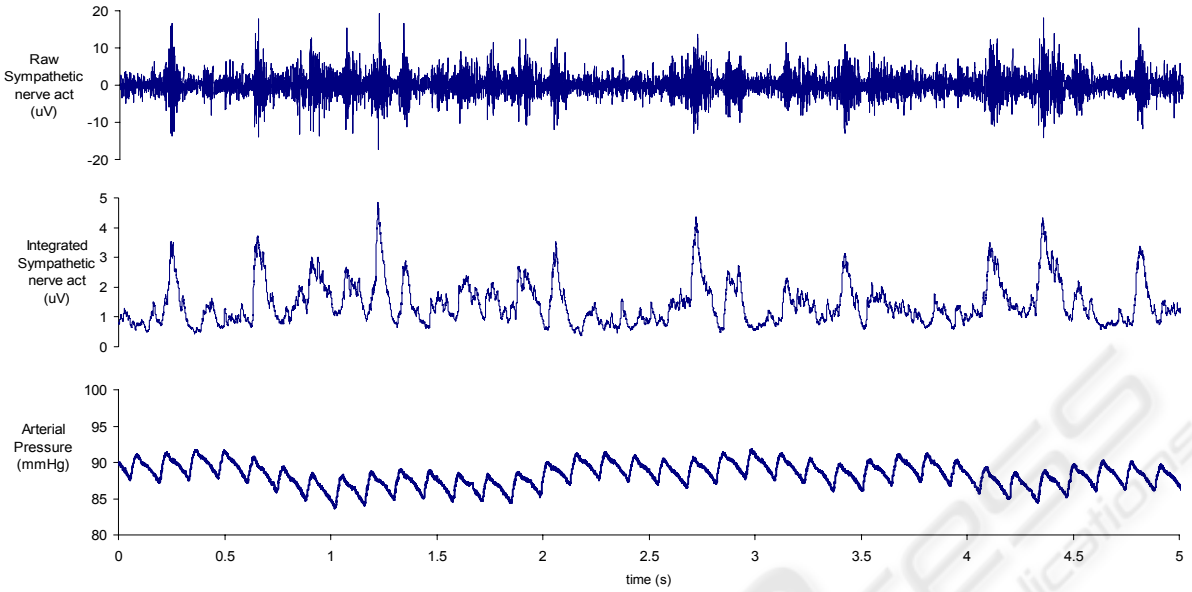

Figure 7: Example from one rat showing raw renal sympathetic nerve activity (top panel), rectified and integrated nerve activity (middle panel) and arterial blood pressure (bottom panel) recorded whilst conscious over a period of 5 s.

Prior to implantation the implant was sterilized in an 8% gluteraldehyde solution overnight and then rinsed in sterile saline. The surgery was performed using sterile procedures on a heated surgical table. Anesthesia was induced by placing the rat in a chamber filled with isoflorane, then a nose cone arrangement was used to maintain the isoflorane anaesthesia at a surgical level. An abdominal incision was made and the abdominal aorta cleared just above the iliac bifurcation. Using silk sutures the aorta was temporarily occluded and a 23 gauge needle used to pierce the aorta. The cannula of the transmitter was inserted into the aorta and advanced approximately 4cm. The cannula was secured in place using cyanoacryalate adhesive and blood flow restored. The body of the transmitter was placed in the abdominal cavity, with the nerve electrodes and ground electrode exteriorized, and the muscle incision closed. A left flank incision was then made and the electrodes tunneled under the skin to this incision. A retroperitoneal incision was made through the muscle and gentle retraction used to expose the kidney. The renal nerve was found near the renal artery and dissected free of the surrounding tissue using fine forceps and visualisation under a surgical microscope. The Teflon coating was removed from the last 3mm of the electrode leads and the stainless steel fashioned into small hooks.The electrode leads were will be sutured to the wall of the artery and the intact nerve placed over the hooks. The nerve/electrode assembly is insulated from the surrounding tissue using silicone elastomer (Kwik-sil, World Precision Instruments).

The muscle layer was then closed, with the earth electrode placed subcutaneously. Then both skin incisions were closed with staples. As soon as a rat regained consciousness it was returned to its home cage. A heating pad was placed under the cage for 24 h after the surgery. Rats received buprenorphine (Temgesic 1 µg/100 g) as an analgesic.

3.2 Results

Figure 7 is an example of data recorded from a conscious unconstrained rat. The recording shows the hallmark traits of SNA, with bursts of activity occurring synchronously with the cardiac cycle (Malpas and Ninomiya 1992). Evident in this trace are small expiration related decreases in blood pressure with a corresponding increase in the bursts of renal sympathetic nerve activity illustrating the arterial baroreflex response and its dependence on renal sympathetic nerve activity (Dorward, Riedel et al. 1985). BP recordings show good fidelity with a crisp reproduction of the diastolic inflection without ringing or undershoot. However, pulse pressure is considerably lower than expected with a peak to peak value of approximately 5 mmHg. The cause of this is unknown, but may be due to the positioning of the catheter or surgery trauma. Further verification of the coordination between blood pressure and SNA are shown in Figure 8 where 500

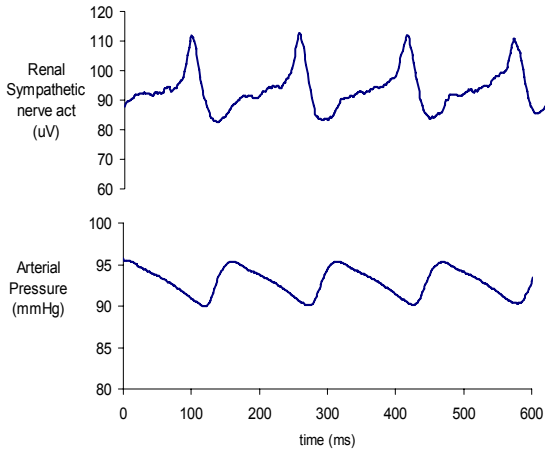

Figure 8: Example from one rat showing renal sympathetic nerve activity (top panel) and arterial blood pressure (bottom panel) averaged over 500 ms synchronized using peak systolic blood pressure.

ms intervals of blood pressure and SNA are averaged using peak systolic pressure as a trigger (similar to the triggering mechanism of an oscilloscope). This figure illustrates that the renal sympathetic nerve exhibited a clear cardiac related rhythm.

4 CONCLUSIONS

An implantable telemeter which simultaneously acquires blood pressure and microvolt level nerve signals has been presented. The telemeter is of a similar size to existing devices but posses many advantages such as inductive charging, digital transmission, and a high bandwidth microvolt input range bio-potential amplifier. Future work will concentrate on miniaturization and ascertaining the long stability of the blood pressure measurement system.

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