

Telemetric monitoring of blood pressure in freely moving mice: a preliminary study

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Summary

This paper describes for the first time the possibility for recording the systolic pressure (SP), diastolic pressure (DP), and the mean arterial pressure (MAP) as well as the heart rate (HR) and locomotor activity (LA) in freely moving mice, using a commercially available telemetry and data acquisition system. The system comprises a new, small radio-telemetry transmitter implanted in the peritoneal cavity, a receiver board placed underneath the home cage, a multiplexer and a computer-based data acquisition system. The signals from the receiver were consolidated by the multiplexer and were stored and analysed by the computer. The telemetered pressure signals (absolute pressure) were corrected automatically for changes in atmospheric pressure measured by an ambient pressure monitor. The effects of implantation on animal behaviour, and, after the animals had recovered, the effects of handling on the SP, DP, MAP and HR were examined. The radio-telemetry system for recording the SP, DP, MAP and HR provides an accurate and reliable method for monitoring the direct effects of handling on SP, DP, MAP and HR. In addition, by using this new blood pressure (BP) transmitter, we maintain that BP measurements in freely moving mice are more efficient, reliable, and less labour-intensive than the measurement techniques described in the literature thus far.

Keywords Operation technique; handling; blood pressure; heart rate; mouse; telemetry

Recent studies have shown that measurements of physiological variables in freely moving mice by using implantable radio-telemetry are more efficient, reliable and less labour intensive than the measurement techniques described in the literature thus far (Clement *et al.* 1989, Kramer *et al.* 1993, Kramer *et al.* 1995, van Acker *et al.* 1995, 1996, Mansier *et al.* 1996, Fewell *et al.* 1997, Stiedl & Spiess 1997, Kramer *et al.* 1998, Uechi *et al.* 1998). For example, our *in vivo* cardiotoxicity studies have shown that mice

equipped with radio-telemetry transmitters to measure electrocardiogram (ECG) and HR can serve as an *in vivo* model for studying doxorubicin-induced cardiotoxicity. This toxicity is generally believed to be caused by the formation of oxygen-free radicals (van Acker *et al.* 1995). From our recent cardiotoxicity studies we have concluded that the ECG measured by radio-telemetry can be considered a valuable and sensitive tool for measuring the cardiotoxic effects of anti-cancer agents and protectors by monitoring the animals as often as necessary during treatment. In addition, telemetry makes it possible to monitor without introducing interfering factors and allows the detection of

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at least 50% protection with only 5–6 animals per treatment group, which is a considerable reduction when compared with other studies in the literature (van Acker *et al.* 1996). In order to extend our research to the effect of oxygen-free radicals on BP, we investigated the possibility of using a new BP radio-telemetry transmitter to measure BP in freely moving mice.

Measurements of BP by radio-telemetry have been described for many animal strains, except mice (Brockway & Hassler 1993). The most common techniques currently employed for monitoring BP in conscious mice are the use of indirect tail cuff plethysmography (Tail-Cuff (TC)) (Krege *et al.* 1995, Esther *et al.* 1996, Gross *et al.* 1997, Schlager & Sides 1997), and the use of direct cannulation with externalization of (fluid-filled) catheters (Intra-Arterial (IC)) (Chen *et al.* 1997, Desai *et al.* 1997, Oliverio *et al.* 1997, Wiesel *et al.* 1997, Mattson 1998). There are considerable drawbacks associated with these methods, which in many respects make each of them undesirable as a means of obtaining accurate pressure measurements (Brockway & Hassler 1993).

In this paper we describe the surgical technique for implanting the small, new radio-telemetry transmitter for measuring BP in mice, and illustrate its use by measuring the SP, DP, and MAP as well as the HR in freely moving mice under various experimental conditions. In addition, this study was set up as an initial evaluation of this technically demanding technique, to illustrate its practicality.

Materials and methods

Animals

Five male mice (Swiss SE, 10–12 weeks old, body weight 30–35 g) were used for the implantation of the transmitters. The animals were obtained from Harlan Netherlands (Harlan Netherlands BV, PO Box 167, 3700 AD Zeist, The Netherlands) and were kept under constant temperature ($22 \pm 2^\circ\text{C}$), humidity ($60 \pm 5\%$), and light–dark periodicity (L:D 12:12; lights on from 07:00 to 19:00 h). The illumination was measured in

the animal room with a lighting-illuminator (model C101, Data Sciences International, St Paul, Minnesota, USA), connected to the data acquisition system. Throughout the experiment, food and water were supplied *ad libitum*. The mice were fed with pellets (RMH-TM 1110; Hope Farms BV, PO Box 85, 3440 AB Woerden, The Netherlands) and housed individually in Macrolon Type III cages.

Transmitter implantation

Preoperation procedures

The new small telemetric transmitter (TA11PA-C20, Data Sciences (DSI), St Paul, Minnesota, USA, Fig 1) was implanted in the peritoneal cavity of the animals through a ventral laparotomy under anaesthesia, with 0.07 ml per 10 g i.p. of a mixture of one part of the sedative/neuroleptic anaesthetic Hypnorm® (0.315 mg/ml fentanyl and 10 mg/ml fluanisone; Janssen Pharmaceutica, B 2340 Beerse, Belgium), one part of the sedative anaesthetic Dormicum® (5 mg/ml midazolam; Roche, PO Box 42, 3640 AA Mijdrecht, The Netherlands), and two parts of sterilized water.

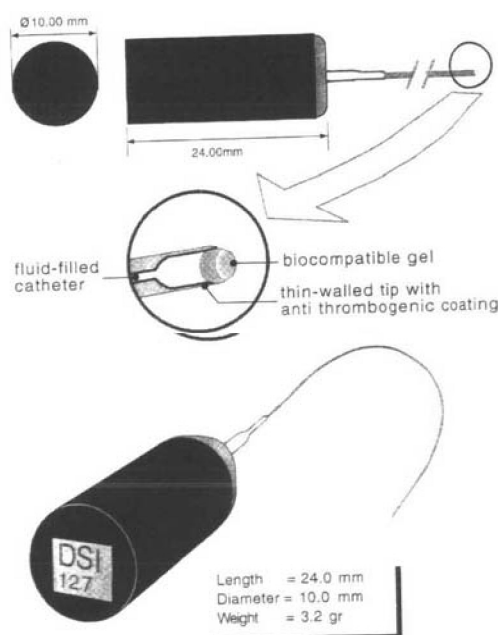


Fig 1 Schematic drawing of the telemetry transmitter which was implanted in the mouse

Before making the incision in the skin of the animal, we used a clipper to remove the hair from the abdominal area of the anaesthetized animal. A cream was used (VEET, Reckitt and Colman, Naarden, The Netherlands) to remove remaining hairs. The animal was placed on a sterile drape under an operation microscope (Zeiss Nederland BV, Weesp, The Netherlands) on a thermostatically controlled warm plate maintained at 36–37°C during the operation, and the operation area was sterilized with iodine.

Operation

A 2–2.5 cm long incision in the skin along the midline of the abdominal skin, immediately caudal to the xiphoid process, was made. Subsequently, the abdominal wall was opened and the intestines were retracted with sterile gauze (Versalon®, Kendall Company, Mansfield, MA 02048, USA) followed by the isolation of the abdominal aorta via blunt dissection. The abdominal aorta was carefully separated from the vena cava just caudal to the point where the left renal vein crosses over the aorta. An occlusion ligature (Perma-Hand Seide 5-0, K870, RB-1, Ethicon GmbH, Norderstedt, Germany) was inserted between the abdominal aorta and the vena cava just caudal to the left renal vein. For relaxing the muscular vessel walls, the exposed vessel was irrigated with 2% lidocaine (Free University Hospital Pharmacy, Free University, 1081 HV Amsterdam, The Netherlands). Once the occlusion suture was in place, tension was applied to occlude the blood flow in the aorta. While the aorta was clamped, a small puncture hole was made in the aorta, 1–2 mm cranial to the iliac bifurcation, with a 25 G hypodermic injection needle bent at a 90 degree angle (Sherwood Medical, D-65824 Schwalbach, Germany). The under side of the needle was used as a catheter introducer, through which the sensor catheter was inserted upwards (5–6 mm) into the vessel, using a pair of vessel cannulation forceps (S & T, Fine Sciences Tools, North Vancouver, BC, Canada). It should be noted that the process of inserting the catheter into the aorta is an intricate manoeuvre and needs to be performed quickly

and efficiently in order to prevent ischaemic-related hind-limb paralysis. After insertion, the catheter entry point was dried with a cotton applicator and the catheter entry site was sealed with a minimal application of tissue adhesive (15–20 µl; Vetbond™, 3M Animal Care Products, St Paul, Minnesota, USA). The tension on the occlusion suture was slowly released, while the catheter entry site was observed for leakage. The aorta was irrigated with 2% lidocaine to relieve vessel spasms and prevent hind-limb ischaemia. Then, a small piece of cellulose paper (fibre patch) was placed across the catheter, followed by the further securing of the catheter with the tissue adhesive. When the catheter was fixed in place, the retraction gauze was removed and the peritoneal cavity was flooded with sterile saline followed by massaging the organs back into place.

The transmitter body was inserted into the peritoneal cavity with the catheter looped caudally. By looping a few sutures through a tab located on the transmitter body, the transmitter was attached to the peritoneal wall while the incision was closed in the abdominal wall with absorbable sutures (Dexon II, 3-0,T-31, DG-Davis and Geck, Lameris, The Netherlands). To complete the operation, the incision in the skin was also closed with absorbable suture (Vicryl, 2-0, FS-1, Ethicon GmbH, Norderstedt, Germany).

The mice were housed in individual cages and kept on a warm plate for the first 48 h in the operation room postoperative. Monitoring of the SP, DP, MAP and HR was started by activating the transmitter and by placing the cage on the receiver.

The telemetry system and data collection

Systolic pressure, DP, MAP, HR, and LA were measured by means of radio-telemetry with transmitters (TA11PA-C20, DSI, St Paul, Minnesota, USA), implanted intraperitoneally as described above. The implantable transmitter consists of a sealed plastic cylinder housing (length 24 mm; diameter 10 mm) with a biocompatible silicone elastomer coating, weighs approximately 3.2 g and has a volume displacement of 1.9 cc. The transmitter contains an amplifier, a battery,

radio-frequency electronics, a low viscosity fluid-filled catheter (diameter 0.4 mm; length 5 cm) attached to the sensor located in the body of the transmitter, and a magnetically activated switch which allows the device to be turned on and off either *in vivo* or *ex vivo*. The tip of the thin-walled section of the catheter is filled with a blood-compatible gel which prevents blood from entering the catheter lumen. The outer surface of the tip comprises a thrombo-resistant coating (Fig 1). The transmitter signals are coded in a pulse position modulated serial bit stream, which is received and monitored by the receiver (RPC-1, DSI, St Paul, Minnesota, USA) placed underneath the animal's cage.

The signals from the receiver were consolidated by the multiplexer (Data Exchange MatrixTM, DSI, St Paul, Minnesota, USA) and were stored and analysed by an IBM-compatible personal computer (Compaq Presario 1510) with analysing software (DataquestTM A.R.T.TM version 1.01, DSI, St Paul, Minnesota, USA). The telemetered pressure signals (the absolute pressure) were corrected automatically for changes in atmospheric pressure as measured by an ambient pressure monitor (APR-1, DSI, St Paul, Minnesota,

USA). The pressure transmitters had been calibrated by the manufacturer DSI and have a continuous-use battery life of up to 8 weeks.

Systolic pressure, DP, MAP, HR and integrated LA were monitored every 5 min for 10 s and stored. SP, DP, MAP, and HR data were extracted from the BP waveform. LA was obtained from the system by monitoring changes in the received signal strength which occur upon the movement of the animal. Changes in signal strength of more than a pre-determined threshold generated a digital pulse which was counted by the acquisition system. It is important to note that for the detection of activity the transmitter has to move. Therefore, with the transmitter implanted in the peritoneal cavity, slight head movements during grooming or eating were not registered as activity.

Results

Three out of five operations were successful. Two mice were euthanized prematurely, one day after implantation, since hind-limb ischaemia was observed, likely due to a direct consequence of surgical errors. After

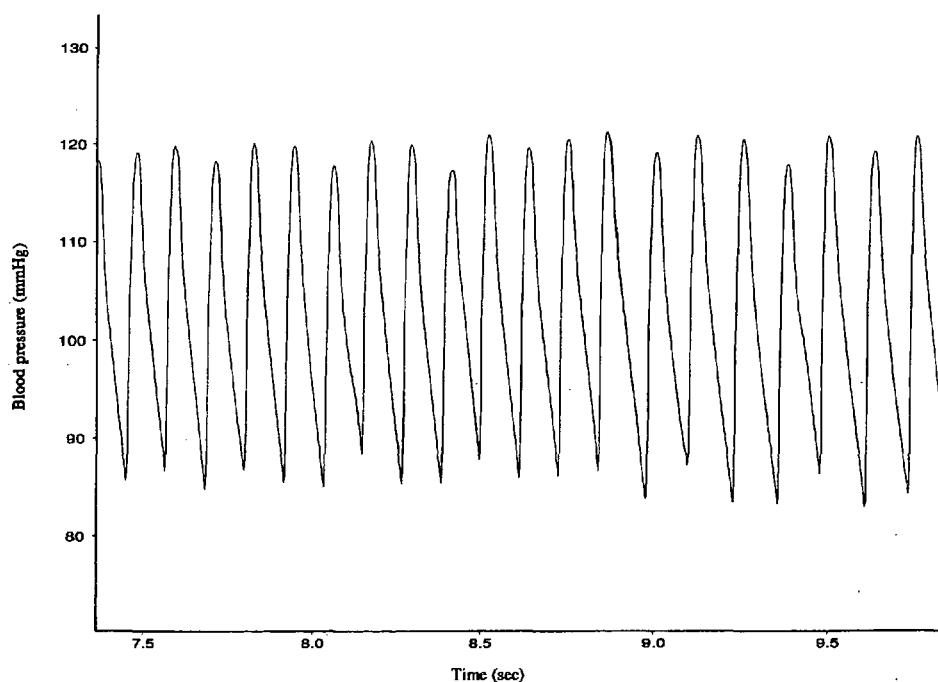


Fig 2 Representative blood pressure waveforms of a mouse while in his home cage. A typical example is shown

Table 1 Heart rate (bpm) and blood pressure (mmHg) measured during various activities of the mice

Activity	Heart rate	Diastolic pressure	Systolic pressure	Mean arterial pressure
During sleep	350–400	70–80	102–112	86–96
At rest (awake)	450–500	75–85	110–117	93–103
After light activity	600–650	94–109	126–138	110–124
During weighing	700–750	105–120	140–155	123–138
During hand restraint	750–800	105–120	140–155	123–138
After placing in a different cage	750–800	105–120	140–155	123–138

The values indicate the range in which the different animals fit at the time of measurements, 2 weeks after the operation. Sampling time every 5 min

surgery, recovery criteria included weight gain after an initial loss (Kramer *et al.* 1993) and changes in behaviour such as building nests with available paper towels. The mice had to recover from their surgical procedure for at least 5–6 days, before they started to demonstrate a normal diurnal rhythm of HR, BP and LA (data not shown). Animals appeared lively throughout the study, and we observed no behavioural differences compared with mice without transmitters.

Figure 2 shows typical representative BP waveforms measured in a freely moving mouse in his home cage. In Table 1 an over-

view of the SP, DP, MAP and HR after various activities is presented. Two weeks after the operation the daily recording was started, and the lowest values in HR (350–400 beats/min), DP (70–80 mmHg), SP (102–112 mmHg) and MAP (86–96 mmHg) were found, as expected, when the mice were sleeping in their home cages (Table 1). Stressful situations such as hand restraint of the animals or placement of the mice in other cages increased the HR to a maximum of 750–800 beats per minute (bpm), the DP to 105–120 mmHg, the SP to 140–155 mmHg and MAP to 123–138 mmHg, respectively.

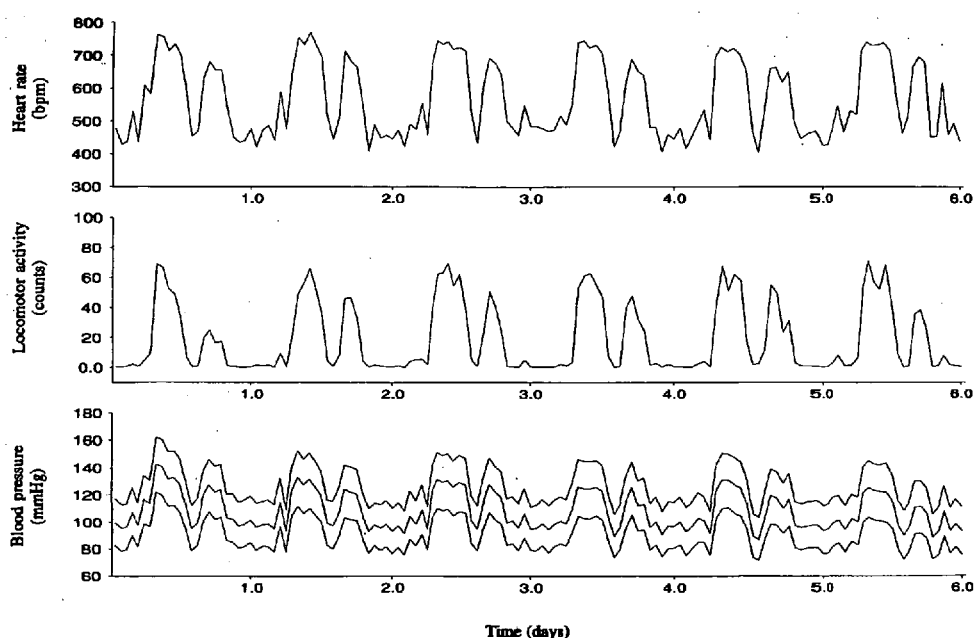


Fig 3 Plot show 24 h circadian rhythms, from six consecutive days of systolic, diastolic, mean arterial pressure, heart rate and locomotor activity of a freely moving mouse using radio-telemetry. The plot represents the mean of the moving average (one hour), and the recordings shown, started 7 days after the implantation

Figure 3 represents the mean of the moving average (1 hour) of 24 h rhythms in SP, DP, MAP, HR and LA of a freely moving mouse as monitored by telemetry. For all three mice in their home cages, 24 h rhythms in HR ranged between 300–600 bpm during day time and 650–800 bpm during night time, the SP between 100–120 mmHg (day time) and 125–155 mmHg (night time), the DP between 70–90 mmHg (day time) and 105–120 mmHg (night time), and MAP between 85–105 mmHg (day time) and 115–138 mmHg (night time), respectively. Circadian rhythms in LA (low during the light period: 07:00 to 19:00 h, and high during the dark period: 19:00 to 07:00 h), could be established in the same mice.

Upon explanation, visual examination of the lower abdominal aorta and abdomen indicated normal fibrotic growth around the body of the device and the presence of intestinal adhesions that normally occur following abdominal surgery. None of the animals indicated abnormal features or discoloration of the abdominal aorta, kidneys or liver. The gastrointestinal tract also appeared to be normal.

Discussion

The two most commonly used alternative measurement techniques for measuring BP in small laboratory animals like mice are indirect tail-cuff plethysmography (TC) and direct measurements by fluid-filled arterial catheters (IA), which are externalized and then connected to pressure transducers, as mentioned in the Introduction section. Brockway and Hassler (1993) described the disadvantages of these methods in their review paper. They mentioned that the fundamental nature of TC is such that measurements can be unreliable or inaccurate if the animal moves, is subjected to loud noises or other stressors, or is vasoconstricted. In the case of IA, the most prominent factor limiting the useful life of this technique is patency of vascular catheters, especially those used for blood withdrawal or pressure measurement. There is also a risk of infection involving exteriorized vascular catheters or lead wires, when using this method

(Brockway & Hassler 1993). Also, Bazil *et al.* (1993) reported that BP and HR remained increased after implanting arterial catheters, and showed in their study with conscious spontaneously hypertensive rats the benefits of using the radio-telemetry system when compared with both the other systems described above.

Radio-telemetry with an implantable transmitter, which minimizes exposure to stress, provides a way of obtaining accurate and reliable measurements from awake and freely moving animals (Lange *et al.* 1991, Bazil *et al.* 1993, Irvine *et al.* 1997) and can be a valuable tool for the pharmacological screening of new compounds (van Acker *et al.* 1995). As described in the Introduction section, the major topic of research of our group is the role of free radicals, with an emphasis on their pharmacology and toxicology.

Measurement of BP via telemetry has been described for small laboratory animals including rabbits (Sato *et al.* 1995, van den Buuse & Malpas 1997), guineapigs (DePasquale *et al.* 1994) and rats (Lemmer *et al.* 1995, van Vliet *et al.* 1996, Irvine *et al.* 1997, Vleeming *et al.* 1997). However, no such measurements have previously been obtained in mice. We have therefore investigated the possibility of using a new commercially available small telemetry transmitter to measure the SP, DP, and MAP in freely moving mice.

The first few days after the implantation of the telemetry transmitter, the animals show inhibited LA and have to recover for at least 5–6 days before a normal diurnal rhythm of SP, DP, MAP, HR and LA is observed, which is completely in agreement with prior mice telemetry studies which also show a normal diurnal rhythm for HR, body temperature and LA several days after the operation (Clement *et al.* 1989, Kramer *et al.* 1993, van Acker *et al.* 1995, Stiedl & Spiess 1997). Also, Baumans *et al.* (1998) showed that after one week of recovery following an intraperitoneal transmitter implantation for measuring ECG, HR, LA and body temperature, the mice cope very well with the weight of the implanted transmitter. No difference in behavioural parameters, such as eating,

drinking, climbing, locomotion, grooming and resting was found after one week when compared with non-implanted animals. It should be noted that the BP transmitter we implanted in our study has the same weight and the same volume displacement as the radio-telemetry transmitter implanted by Baumans *et al.* (1998).

There are few studies documenting the accuracy of the alternative measurement techniques (TC and IC methods) for measuring BP in mice. Krege *et al.* (1995) reported HR differences between the two methods. The systematically higher HR in mice, when evaluated by the TC method, might reflect a stress response to restraint and heating and/or might reflect residual HR-lowering effects of anaesthesia in the IC group. Krege *et al.* (1995) also showed, however with a small difference between both groups, that the tail-cuff heart rates in an untrained group of mice were significantly increased compared with heart rates in the trained group of mice (711 ± 4.8 compared with 698 ± 3.6 bpm). Both values are in accordance with the higher HR values we found by radio-telemetry (Table 1) during the several activities, indicating that the TC method is apparently very stressful for the animals, in spite of the extensive training as described in the Material and Methods section of their paper. In Table 1, the direct effects of handling on the BP of the mice are summarized. It seems that even a small change in activity, like that from rest (DP 75–85 mmHg, SP 110–117 mmHg and MAP 93–103 mmHg) to movement (DP 94–109 mmHg, SP 126–138 mmHg and MAP 110–124 mmHg), increases the BP. Handling of the animals will enhance the BP even to the maximum of 105–120 mmHg for DP, 140–155 for SP and 123–138 for MAP, respectively.

Recently, Mattson (1998) described a technique for the direct daily measurement of arterial blood pressure in free-moving, conscious, Swiss-Webster mice. The catheters used in this study were chronically implanted in the femoral artery and vein, tunnelled subcutaneously, exteriorized at the back of the neck in a lightweight tethering string, and attached to a swivel device at the top of the cage. Stable values of MAP

(116 ± 1 mmHg) and HR (627 ± 21 bpm) were shown at rest, however, both values are higher than the values we found at rest with the new device (MAP 93–103 mmHg and HR 450–500 bpm, respectively), which may indicate that the IA method is also stressful for the animals.

In conclusion, it appears to be possible to effectively implant a BP radio-telemetry transmitter to monitor BP, HR, and LA in freely moving mice. The most important advantage is the possibility of the direct and accurate measurement of the effects of cardiovascular drugs, and the freedom from the artefacts which cause the added stress as seen with conventional measurement techniques. By using implanted radio-telemetry, measurements from freely moving animals are more efficient, reliable and less labour intensive than the measurement techniques described in the literature thus far and may better predict the clinical usefulness of e.g. potential anti-hypertensive agents and/or, as in our research, radical scavengers. Apparently, acute effects of drugs on the BP cannot be easily quantified with radio-telemetry, because every handling appears to be a stressful situation for the mice, which results in an increase in BP. Thus, measurements can best be done when the mice rest, and in their home cages without disturbing them.

The greatest challenge in using this new device is the difficulty of the surgical procedure. The small size and delicate nature of the arteries of the mouse require excellent hand-eye coordination and a steady hand in order to successfully catheterize the vessel.

References

- Baumans V, Bouwknecht JA, Boere H, Kramer K, van Lith HA, van de Weerd HA, van Herck H (1998) Intraperitoneal transmitter implantation in mice: effects on behavioural parameters and body weight. *Proceedings Measuring Behavior '98*, Groningen, The Netherlands, p. 85
- Brockway B, Hassler CR (1993) Cardiovascular measurements in pharmacology and toxicology. In: *New Technologies and Concepts for Reducing Drug Toxicity* (Salem H, Baskin SI, eds). Boca, FL: CRC Press, pp 109–32

- Bazil MK, Krulan C, Webb RL (1993) Telemetric monitoring of cardiovascular parameters in conscious spontaneously hypertensive rats. *Journal of Cardiovascular Pharmacology* **22**, 897–905
- Chen XM, Li WG, Yoshida H, Tsuchida S, Nishimura H, Takemoto F, Okubo S, Fogo A, Matsusaka T, Ichikawa I (1997) Targeting deletion of angiotensin type 1B receptor gene in the mouse. *American Journal of Physiology—Renal Fluid and Electrolyte Physiology* **41**, F299–304
- Clement JG, Mills P, Brockway B (1989) Use of telemetry to record body temperature and activity in mice. *Journal of Pharmacological Methods* **21**, 129–40
- Desai KH, Sato R, Schauble E, Barsh GS, Kobilka BK, Bernstein D (1997) Cardiovascular indexes in the mouse at rest and with exercise—new tools to study models of cardiac disease. *American Journal of Physiology—Heart and Circulatory Physiology* **41**, H1053–61
- DePasquale MJ, Ringer LW, Winslow RL, Buchholz RA, Fassa AA (1994) Chronic monitoring of cardiovascular function in the conscious guinea pig using radio-telemetry. *Clinical and Experimental Hypertension* **16**, 245–60
- Esther CR, Howard TE, Marino EM, Goddard JM, Capecchi MR, Bernstein KE (1996) Mice lacking angiotensin-converting enzyme have low blood pressure, renal pathology, and reduced male fertility. *Laboratory Investigation* **74**, 953–65
- Fewell JG, Osinska H, Klevitsky R, Ng W, Sfyris G, Bahrehmand F, Robbins J (1997) A treadmill exercise regimen for identifying cardiovascular phenotypes in transgenic mice. *American Journal of Physiology* **273**, H1595–605
- Gross V, Lippoldt A, Luft FC (1997) Pressure diuresis and natriuresis in doca-salt mice. *Kidney International* **25**, 1364–68
- Irvine RJ, White J, Chan R (1997) The influence of restraint on blood pressure in the rat. *Journal of Pharmacological and Toxicological Methods* **38**, 157–62
- Kramer K, van Acker SABE, Voss H-P, Grimbergen JA, van der Vijgh WJF, Bast A (1993) Use of telemetry to record electrocardiogram and heart rate in freely moving mice. *Journal of Pharmacological and Toxicological Methods* **30**, 209–15
- Kramer K, van Acker SABE, Grimbergen JA, van den Berg D-J, van der Vijgh WJF, Bast A (1995) Effect of dimethyl sulfoxide (DMSO) on the electrocardiogram (ECG) in freely moving male Balb/c mice. *General Pharmacology* **26**, 1403–7
- Kramer K, Voss H-P, Grimbergen JA, Bast A (1998) Circadian rhythms of heart rate, body temperature and locomotor activity in freely moving mice measured with radio telemetry. *Lab Animal* **32**, 162–4
- Krege JH, Hodgin JB, Hagaman JR, Smithies O (1995) A noninvasive computerized tail-cuff system for measuring blood pressure in mice. *Hypertension* **25**, 1111–15
- Lange J, Brockway B, Azar S (1991) Telemetric monitoring of laboratory animals: an advanced technique which has come of age. *Lab Animal* **20**, 28–33
- Lemmer B, Witte K, Minors D, Waterhouse J (1995) Circadian rhythms of heart rate and blood pressure in four strains of rat: differences due to, and separate from, locomotor activity. *Biological Rhythm Research* **26**, 493–504
- Mansier P, Medigue C, Charlotte N, Vermeiren C, Coaboeuf E, Deroubai E, Ratner E, Chevalier B, Clairambault J, Carre F, Dahkli T, Bertin B, Briand P, Strosberg D, Swynghedauw B (1996) Decreased heart rate variability in transgenic mice over-expressing atrial β_1 -adrenoceptors. *American Journal of Physiology* **271**, H1465–72
- Mattson DL (1998) Long-term measurement of arterial blood pressure in conscious mice. *American Journal of Physiology* **274**(2 Pt 2), R564–70
- Sato K, Chatani F, Sato S (1995) Circadian and short-term variabilities in blood pressure and heart rate measured by telemetry in rabbits and rats. *Journal of the Autonomic Nervous System* **54**, 235–46
- Schlager G, Sides J (1997) Characterization of hypertensive and hypotensive inbred strains of mice. *Laboratory Animal Science* **47**, 288–92
- Stiedl O, Spiess J (1997) Effect of tone-dependent fear conditioning on heart rate and behavior of C57BL/6N mice. *Behavioral Neuroscience* **111**, 703–11
- Oliverio MI, Best CE, Kim HS, Arendshorst WJ, Smithies O, Coffman TM (1997) Angiotensin II responses in AT(1A) receptor-deficient mice—A role for AT(1B) receptors in blood pressure regulation. *American Journal of Physiology—Renal Fluid and Electrolyte Physiology* **41**, F515–20
- Uechi M, Asai K, Osaka M, Smith A, Sato N, Wagner TE, Ishikawa Y, Hayakawa H, Vatner DE, Shannon RP, Homcy CJ, Vatner SF (1998) Depressed heart rate variability and arterial baroreflex in conscious transgenic mice with overexpression of cardiac G_{sa} . *Circulation Research* **82**, 416–23
- van Acker SABE, Kramer K, Grimbergen JA, van der Berg D-J, van der Vijgh WJF, Bast A (1995) Monohydroxyethylrutoside as protector against chronic doxorubicin-induced cardiotoxicity. *British Journal of Pharmacology* **115**, 1403–7
- van Acker SABE, Kramer K, Grimbergen JA, van der Berg D-J, van der Vijgh WJF, Bast A (1996) Doxorubicin-induced cardiotoxicity monitored by ECG in freely moving mice. A new model to test potential protectors. *Cancer Chemotherapy and Pharmacology* **38**, 95–101

- van den Buuse M, Malpas SC (1997) 24-hour recordings of blood pressure, heart rate and behavioral activity in rabbits by radio-telemetry: effects of feeding and hypertension. *Physiology and Behavior* **62**, 83–9
- van Vliet BN, Hu L, Scott T, Chafe L, Montani J-P (1996) Cardiac hypertrophy and telemetered blood pressure 6 wk after baroreceptor denervation in normotensive rats. *American Journal of Physiology* **271**, R1759–69
- Vleeming W, van de Kuil A, Te Biesebeek JD, Meulenbelt J, Boink ABTJ (1997) Effect of nitrite on blood pressure in anaesthetized and free-moving rats. *Food and Chemical Toxicology* **35**, 615–19
- Wiesel P, Mazzolai L, Nussberger J, Pedrazzini T (1997) Two-kidney, one clip and one-kidney, one clip hypertension in mice. *Hypertension* **29**, 1025–30