Direct Recording of Renal Sympathetic Nerve Activity in Unrestrained, Conscious Mice

Shereen M. Hamza, John E. Hall

Abstract—Renal sympathetic nerve activity (RSNA) has been measured in anesthetized mice. However, anesthesia and acute surgical preparation cause poor cardiovascular stability and unphysiological blood pressures. This compromised physiological state confounds proper interpretation of experimental results considering the inseparable link between cardiovascular status and autonomic nervous tone. We, therefore, developed a surgical and experimental protocol for measuring RSNA in conscious, unrestrained mice. Male C57Bl/6J mice were chronically instrumented with blood pressure radiotelemeters, an indwelling jugular venous catheter and a bipolar electrode for recording RSNA. Mice were placed in a home cage and left to recover for 48 to 72 hours. Survival rate was 100%; all of the mice exhibited normal behavior with no sign of distress 24 hours after surgery. RSNA was successfully recorded in 80% of the mice at 48 and 72 hours postsurgery; viable RSNA was reduced to 70% and 50% at 4 and 5 days postsurgery, respectively. Mean arterial pressure (116±2 mm Hg; n=10) was consistent with values reported previously for conscious mice. RSNA increased with the normal physical activities of eating and grooming and was validated by ganglionic blockade and pharmacological manipulation of blood pressure; reduction in blood pressure to 62±3 mm Hg with nitroprusside increased RSNA by 77±9% above baseline (n=5; P<0.05), whereas an increase in blood pressure to 137±6 mm Hg with phenylephrine reduced RSNA by 79±2% compared with baseline (n=5; P<0.05). Thus, we demonstrate an accessible and effective method for direct assessment of RSNA in conscious, unrestrained mice. (Hypertension. 2012; 60:856-864.)

Key Words: autonomic tone ■ physiological blood pressure ■ kidney

Materials and Methods

All of the experimental procedures are in accordance with the National Institutes of Health Guide for the Care and Use of

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Animals and Housing

Twelve Male C57BL/6J mice (24–35 g, Jackson Laboratories) were housed for ≥1 week in the laboratory animal facility on arrival at the University of Mississippi Medical Center. They were maintained on standard rodent chow and tap water ad libitum in a temperature- and humidity-controlled environment before and after surgery.

Construction of the Implantable RSNA Electrode

Three lengths (250-mm each) of Teflon-coated stainless steel, multiple stranded wire (0.001-in bare, 0.0055-in coated; A-M Systems, Inc), were cut, and 15 mm of the Teflon coating was stripped away from one end with a #11 scalpel blade to expose the metal wires. The bared ends of 2 of the lengths of wire were each soldered to a single male pin connector (brass with gold plating; A-M Systems, Inc) to create the bipolar electrode leads (Figure 1A). A 20-mm piece of heat shrink tubing (1.6-mm diameter, RadioShack) was slipped over the pin connector and wire to cover the newly soldered joint while exposing the pin tip. The tubing was shrunk over a heat gun to insulate the connection between the wire and pin connector. The unexposed ends of the 2 electrode leads and the third length of Teflon-coated wire (ground wire) were then threaded together through a length of polyethylene tubing (Figure 1B; 200-mm long, polyethylene (PE) 90, ID 0.86 mm, OD 1.27 mm, Braintree Scientific). Of the 3 wires, the ground wire was identified and pulled through the PE 90 sheath a little further to differentiate it from the bipolar electrode leads.

Under a dissecting microscope, the 3 loose ends of the electrode were threaded through a 5-mm–long piece of smaller polyethylene tubing (PE 10, ID 0.28 mm, OD 0.61 mm, Braintree Scientific; the purpose of which is to bind the leads together). Similarly, a 1.5-mm piece of this PE tubing was threaded onto the 3 wires to rest 2 mm from the first piece. A second 1.5-mm piece of PE 10 was threaded onto the 2 electrode leads to cover the tips and to separate them from the ground wire (Figure 1C). The wires were trimmed such that 2 mm of the bipolar leads would form the surface for contact with the nerve. All of the pieces of PE 10 tubing were secured to the electrode leads with a small drop of Super Glue (liquid; Loctite). Once the super glue was dry (overnight), the Teflon coating was stripped from the bipolar electrode tip and ground wire tip with a #11 scalpel blade, with care taken not to fray the multiple stranded wires. The electrode tip was then bent at a 90° angle at the junction of the 5.0-mm and 1.5-mm PE 10 anchors (Figure 1D). A pedestal to help stabilize the electrode leads to the animal was constructed from 1 inch of polyethylene tubing (2.70 mm ID×4.00 mm OD, Scientific Commodities, Inc), which had been melted at one end to create a flange. This pedestal was threaded onto the electrode and left until needed. This pedestal plus the PE 90 cover protected the electrode so that a spring was not needed and instead used to protect the jugular venous catheter (see below). The electrodes were then packaged and ozone sterilized (TSO₂) before implantation.

Anesthesia and Surgery

Anesthesia was induced with 4% isoflurane and subsequently maintained with 1.5% to 2.0% isoflurane. Body temperature was maintained with 1.5% to 2.0% isoflurane. Body temperature was maintained with Deltaphase isothermal heat pads (Braintree Scientific). All of the surgical procedures were conducted under aseptic conditions. Immediately on induction of anesthesia, glycopyrrolate (50–70 μg/kg, SC) was administered to prevent production of excessive airway secretions. This dose of glycopyrrolate was administered once again at the midpoint of the surgical procedure.

Implantation of the RSNA Electrode

The mouse was positioned on his right side; the rostral end at the surgeon’s left, exposing the left flank. A small incision (<5 mm) was made in the skin dorsally, 1 cm below the scapulae; this is the exit site for the renal sympathetic nerve electrode leads. A second incision (<20 mm) was made perpendicular to the spine in the skin overllying the left flank, 2 mm caudal to the ribs. A 13G stainless-steel needle was tunneled subcutaneously from this flank incision to the dorsal exit site. The RSNA electrode was threaded into the 13G needle, which was pulled back to leave the electrode tip on the abdominal muscle of the left flank, with leads tunneled subcutaneously to exit dorsally. The electrode tip was placed to the side and an incision was made in the abdominal muscle. Using small-tipped cotton applicators, the fat and connective tissue along the back muscle were gently separated to retroperitoneally expose the left kidney. Steel microretractors were used to gently open the surgical field and retract the kidney, with great care taken to avoid damage to the renal parenchyma.
stretching the renal neurovascular bundle or damaging the kidney itself.

The renal neurovascular bundle was visualized with a high-power dissecting microscope (Leica M80, Leica Microsystems). A renal nerve bundle was identified coursing alongside the renal artery and vein and was gently isolated from the surrounding tissues with fine, straight forceps (#5 Medical and #5 Medical Biology, FST by Dumont, Fine Science Tools). It is imperative that the nerve is not stretched or picked up with forceps during this isolation. In addition, damage to the renal lymph duct generally running along the renal vessels was also avoided, because this will lead to continuous leakage of lymph fluid in the area, which will inevitably interfere with the nerve signal. The renal nerve bundle was left intact and not sectioned to maintain long-term viability of the nerve and to help maintain stable contact between the nerve and electrode. At this point, the electrode tip was introduced into the abdomen and its position adjusted such that the bipolar electrode tip and ground wire laid perpendicular to the renal nerve bundle; the ground wire must have good contact with the underlying tissues and the electrode must not hamper the renal circulation (Figure 1D). The renal nerve bundle was gently lifted with angled forceps (#5/45, FST by Dumont, Fine Science Tools), and the electrode tip was carefully slipped underneath the nerve, leaving it in direct contact with both electrode wires. A small piece of Parafilm was placed between the nerve/bipolar wires and the third (ground) wire (Figure 1D); all of the fluid around the nerve and electrode was removed with small absorbent sponges (Fine Science Tools). A 2-component silicone elastomer (Kwik-Sil, World Precision Instruments) was applied to the nerve/electrode unit, ensuring that the silicone pooled under and around the nerve for full electric insulation (not just on the surface of the nerve). After the silicone cured completely (~1–2 minutes), the very edges of the silicone “blob” were carefully lifted with forceps and fixed to the surrounding tissue with a small amount of surgical adhesive (Vetbond, 3M). The abdominal muscle was then closed with discontinuous absorbable sutures (5-0 Polysorb absorbable suture, Tyco Healthcare); the overlying skin was similarly sutured closed.

**Implantation of Radiotelemeter and Jugular Venous Catheter**

A midline incision was made in the skin of the neck region, and the underlying glandular tissue was separated by blunt dissection to expose the muscles of the neck. The left carotid artery was exposed by blunt dissection and carefully separated from the vagus nerve. Three 6-0 silk sutures (Deknatel, Braintree Scientific) were passed underneath the artery with the rostral-most suture occlusively tied around the vessel. The middle and caudal-most sutures were loosely tied. Rostral and caudal sutures were retracted and a small incision made in the artery for introduction of the radiotelemeter catheter (Model TA11-PAC10, Data Sciences International). The catheter was inserted 10 mm and sutured in place. The telemeter body was tunneled to a subcutaneous pocket along the right flank.

The right jugular vein was exposed by blunt dissection, and 2 pieces of 6-0 silk suture were threaded around the vessel. The rostral suture was tied to completely occlude the vessel, and the caudal suture was used for temporary retraction. The vein was then catheterized with heat-stretched rena-pulse tubing (RPT-040, Braintree Scientific); the catheter was advanced ~8 mm into the vessel and secured to the surrounding tissues by tying the 6-0 sutures around the catheter and also application of an adhesive containing cyanoacrylate (SuperGlue Gel, Loctite). The mouse was turned onto the left side, and a 13G stainless-steel needle was used to tunnel the catheter from the neck to its exit point in the midscapular region. The neck incision was closed with discontinuous sutures (5-0 Polysorb, Tyco Healthcare); with the animal in the prone position, a small subcutaneous button (Instech Solomon) covered in Dacron material was threaded onto the venous catheter and secured under the skin with sutures. A stainless-steel spring was threaded over the venous catheter and secured to the skin button to protect the catheter.

The polyethylene pedestal of the electrode was then secured to the underlying muscle with surgical adhesive (Vetbond, 3M) with overlapping skin sutured over the flange for further support. Antibiotic ointment was applied to all of the incisions (Triple Antibiotic Ointment, Fougera). Carprofen was administered (1 mg/kg SC) for analgesia. The mice were placed in metabolic cages lined with wood chip bedding and paper towel to recover. Electrode leads were coiled outside the cage until the time of the experiment. The cages were placed on a warm heat pad for the first 24 hours of recovery. Once the mice recovered fully from anesthesia, food and water were provided ad libitum.

**Experimental Setup**

A stainless-steel top antivibration table was electrically grounded and fitted with a simple Faraday cage constructed from a wooden frame and aluminum screen mesh. Forty-eight to 72 hours postsurgery, the home cage housing the mouse was placed on a radiotelemetry receiver (PhysioTel Receiver, model RPC-1, Data Sciences International) within the Faraday cage. This receiver was connected to a Pressure Output Adapter (model R11CPA, Data Sciences International), which was, in turn, connected to a PowerLab data acquisition system for recording of blood pressure (LabChart 7 software, ADInstruments). To record RSNA, the electrode leads were uncoiled and the pin connectors were plugged into complementary female pin connectors (brass with gold plating, A-M Systems Inc), which had been soldered previously to the ends of paired,
shielded PVC insulated cable (PVC Audio Connection Cable, 32 AWG, Belden). The opposite ends of this paired cable were soldered to banana plugs, which were connected to a preamplifier (×10 amplification, model 4002, Dagan Corporation). The ground wire was connected to the ground pole of this preamplifier. The preamplifier was connected to a differential amplifier (EX4-400, Dagan Corporation), and the nerve signal was amplified (×10000) and filtered (low cut, 100 Hz; high cut, 1000 Hz). Signals were displayed and recorded on a PC online, simultaneously with blood pressure data.

Experimental Protocol
Mice were unrestrained and housed in their home cages with free access to food and water at all times. After surgery, mice were housed in the same temperature- and humidity-controlled room in which RSNA recording was to take place. At the time of the experiment (48 hours after surgery), 30 minutes of stabilization was allowed before recording of baseline blood pressure and RSNA data. At this time, a bolus of sodium nitroprusside (2.5 μg/g of body weight in a volume of 25 μL of saline) was slowly administered in the infusion line followed by 50 μL of saline. Blood pressure and RSNA were recorded for 2 to 5 minutes, at which time a bolus of phenylephrine (20 μg/g of body weight in 25 μL of saline) was similarly administered in the infusion line. Blood pressure and RSNA were recorded for an additional 10 to 15 minutes. During this procedure, mice were quiet and still. To verify the postganglionic nature of the nerve signal, we also injected the ganglionic blocker hexamethonium (50 μg/g IV in 25 μL of saline). The background noise for the nerve activity trace was estimated from the residual activity remaining after ganglionic blockade with hexamethonium or during postmortem recording of RSNA for 30 minutes after the mice were euthanized with an overdose of isoflurane.

Data Analysis
LabChart 7 software was used to analyze raw blood pressure and RSNA traces. Blood pressure and RSNA data were recorded simultaneously using LabChart 7 software and a PowerLab data acquisition system at 1000 samples per second. Although we used Data Sciences International radiotelemeters to measure blood pressure, we used a Blood Pressure Output Adapter with Ambient Pressure Reference (models R11CPA and APR-1, Data Sciences International) to feed the signal directly to the PowerLab system for...
simultaneous recording with RSNA. The raw trace was digitally integrated and full-wave rectified using this software: Absolute Integral was selected for the integral settings with a time constant decay of 0.1 seconds. The integrated RSNA signal (in μV·s) was analyzed for each portion of the experimental protocol, with ≥3 measurements taken for baseline and experimental periods. RSNA was analyzed at the maximum blood pressure response to PE and sodium nitroprusside. These individual measurements were averaged for each portion of the experimental protocol to give a single value. Quantification of the experimental responses of RSNA was achieved by calculating the percentage change of RSNA from baseline, which we designated as 100%. Statistical analysis of the response of RSNA to sodium nitroprusside and phenylephrine was completed with a Student t test; significance was accepted with P values <0.05.

Results

Of the 12 mice instrumented for this study, all survived and tolerated the surgical procedure well to give a survival rate of 100%. By 24 hours after successful surgery, these animals showed no sign of pain or distress and clearly exhibited normal curiosity, as well as typical grooming and feeding behavior. Ten of these 12 mice showed a true, high-quality RSNA signal 48 hours after surgery. The RSNA signal remained 3 days after surgery in all 10 of the mice; however, the number of animals with a recordable RSNA was reduced to 7 (70%) and 5 (50%) by 4 days and 5 days postsurgery, respectively. Although the remaining animals did not show a reasonable RSNA signal because of excessive noise or contamination by ECG signals, they were all in good health until euthanization.

Mean arterial pressure for animals with viable RSNA was 116±2 mm Hg, with an average heart rate of 596±22 bpm (n=10) 48 hours after surgery. A representative recording of blood pressure and RSNA 48 hours after recovery shows rhythmic bursts of RSNA clearly visible above the background noise (Figure 2). Renal sympathetic activity also increased with activity as shown in mice that were actively grooming or eating (Figure 3). RSNA was also clearly discernable for ≥5 days after surgery in half of the mice studied (Figure 4). Blood pressure and heart rate values for these mice over the course of the 5 days was stable and did not change significantly.

Figure 4. Sequential representative traces of blood pressure and renal sympathetic nerve activity (RSNA) in 1 conscious, resting mouse several days after surgical preparation, (A) 2 days, (B) 3 days, (C) 4 days, and (D) 5 days postsurgery.

Table. Baseline Mean Arterial Pressure and Heart Rate Values in Instrumented Mice Over 5 Consecutive Days Postsurgery

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not differ from values obtained previously in our hands in mice allowed 8 to 10 days of recovery from surgery (Table).\(^5\)

Verification of true RSNA entrained with the arterial baroreflex was completed by manipulating blood pressure with sodium nitroprusside and phenylephrine; RSNA increased in response to the reduction in blood pressure induced by sodium nitroprusside and was effectively silenced after elevation of blood pressure with phenylephrine (Figure 5). Reduction of blood pressure to \(62\pm3\) mm Hg with sodium nitroprusside increased RSNA to \(77\pm9\%\) above baseline (\(n=5; P<0.05\)); subsequent elevation of blood pressure to \(137\pm6\) mm Hg with phenylephrine reduced RSNA to \(79\pm2\%\) below baseline values (\(n=5; P<0.05\); Figure 6). Ganglionic blockade with hexamethonium eliminated the RSNA signal, which was no different from the residual postmortem recording (Figure 7).

Discussion

We have described and validated a method for directly recording RSNA in conscious, freely moving mice. Animals instrumented with a telemetric blood pressure recording device, an indwelling catheter for intravenous infusion, and exteriorized electrode leads for transmission of RSNA were allowed to recover from surgery, undisturbed for 48 to 72 hours in their home cage. Subsequent experimental manipulations by the investigator were remote and did not perturb the animals, which remained in the home cage with free access to food and water at all times. Thus, this method eliminated the physiological effects of anesthesia and sources of stress to the animal, which unavoidably confound interpretation of sympathetic nerve activity data.

All of the mice instrumented for RSNA and blood pressure recording exhibited normal behavioral characteristics, such as...
eating, grooming, alertness, and curiosity, 24 hours after surgical instrumentation. Although the recovery time required for full restoration of normal cardiovascular parameters, such as blood pressure, after implantation of telemetric recording devices has been reported to be as long as 7 days, in our hands normal blood pressure is restored much sooner, and the values for blood pressure and heart rate reported here are comparable to similarly instrumented animals in our hands that were allowed to recover for 8 to 10 days. The use of telemetric devices for blood pressure measurement is advantageous not only for the reduction of stress in our animals but also for improved quality of the blood pressure signal with preserved pulse pressures and reliable heart rate and blood pressure values. The use of telemetry also eliminates the need for periodic catheter flushing (and use of the heparinized fluid that this often entails), as well as unnecessary perturbation of the animal during the experimental protocol. The indwelling venous catheter and renal sympathetic nerve electrode leads were also fully exteriorized at the time of surgery rather than temporarily stored in a subcutaneous pocket to avoid reanesthesia of the animals, however brief, and any pain or distress directly before the time of the experiment.

We have shown bursts of RSNA that are clearly visible above background noise in a resting animal; this RSNA subsequently increased during natural behavior, such as eating and grooming, by the animal as expected. For analytic purposes, we deliberately focused on periods of time when the animal was quietly resting or sleeping and excluded periods of movement to avoid possible misinterpretation of experimental results because of natural increases in sympathetic tone during eating, physical activity, or even curiosity and alertness by the animal. Other potential sources of misinterpretation include signal contamination with ECG pulses or excessive movement of the electrode leads (which appears as a “wavering” baseline); these periods should also be excluded from analysis. Importantly, we demonstrated that we have recorded true RSNA, which is entrained by the arterial baroreflex, as shown by increased RSNA on reduction of blood pressure with sodium nitroprusside and the virtual elimination of RSNA on an ensuing phenylephrine-induced rise in blood pressure. That the arterial baroreflex was clearly intact in our model also directly addresses concerns regarding the occlusive implantation of the blood pressure transmitter catheter in the left carotid artery and any potential cardiovascular disturbance that this may cause. Elimination of the nerve signal after ganglionic blockade also verified the postganglionic nature of the signal.

Although our ability to obtain a reliable RSNA signal diminished over several days after surgical preparation, we were able to reliably record RSNA for 3 days in all of the mice and for ≤5 days in some of the animals. This allows the possibility to record multiple trials in 1 animal (ie, experimental versus time control) provided that the order of the trials is randomized and baseline parameters are always recorded at the start of each individual trial. Inherent limitations to this technique that may preclude simple day-to-day and between-animal comparisons include natural differences in the number of isolated renal nerve fibers between animals, as well as physical changes that occur over time, such as shifting contact between the nerve bundle and electrode and potential loss of viable nerve fires within the nerve bundle. Nevertheless, we strive to improve this technique to be able to record viable RSNA over several weeks, as has been demonstrated by the excellent work of Miki and colleagues in the rat and briefly outlined by this group in mice.

The growing popularity of genetically modified mouse models in biomedical research has driven a need for the development of methods that enable reliable, feasible, and accurate cardiovascular and autonomic phenotyping of these animals. To our knowledge, there has been only 1 report of measurement of sensory nerve activity in conscious mice. In this study, bladder sensory nerve activity was recorded, and the mice were subjected to anesthesia and surgical exteriorization of indwelling catheters immediately before the experiment and were placed in physical restrainers for the duration of the protocol. Although the mild anesthesia and surgical manipulation before the recording are not ideal and may not impact the final results, restraining the rodents for the duration of the recording is a known source of stress. In addition, only afferent rather than intact nerve activity, which would include efferent traffic, was measured, in contrast to our intact renal nerve preparation. To date, examination of the contribution of the sympathetic nerves to various aspects of physiology and disease in mice has been exclusively completed in anesthetized models. Careful examination of the literature reveals a plethora of types of anesthesia (injectable, inhalational), anesthetic combinations, and doses used in mice. One factor in common with these studies is either the complete absence of blood pressure measurement or reporting of low blood pressures; often despite careful maintenance of core body temperature and artificial cardiovascular support with intravenous fluid infusion (saline or volume expanders) or other measures, such as direction of a stream of oxygen to the animal’s nose. When attempting to eluci-
date the role of the autonomic nervous system in various mouse models, a physiologically normal blood pressure is imperative. Blood pressure and autonomic tone are intimately linked, with increases or decreases in blood pressure resulting in concomitant alterations in sympathetic tone. Some types of anesthesia, however, may markedly reduce sympathetic activity. Although these experiments in anesthetized mice typically compare all experimental values to a recorded baseline nerve activity, it may be difficult to study factors that result in subtle changes in neural tone considering the altered state of the autonomic system.

Although refined surgical skill is necessary for the preparation of mice for conscious nerve recordings, use of this method avoids the limitations of several indirect assessments of autonomic control. Measurement of plasma catecholamine levels in mice is hampered by the wide variation in catecholamine levels in this species, as well as changes related to sampling from anesthetized animals or the route of blood sampling (ie, tail versus indwelling catheter). Akin to plasma catecholamine levels, use of pharmacological agents to block the autonomic nervous system reveals global but not discrete contributions of autonomic tone. Although spectral analysis of blood pressure and heart rate variability is commonly used to estimate autonomic tone in humans and is now often used for rodents, it appears that this may not be as useful in the evaluation of autonomic balance in mice.

Figure 7. Representative trace of blood pressure and renal sympathetic nerve activity (RSNA) at (A) baseline, (B) immediately after ganglionic blockade with hexamethonium (50 μg/g), and (C) postmortem.
Direct measurement of nerve activity in conscious mice comfortable at rest preserves the natural state of the animal as much as possible and allows for the evaluation of specific populations of nerves to different physiological phenomena.

**Perspectives**

It is now possible to routinely measure RSNA directly in conscious mice chronically instrumented for telemetric measurement of blood pressure and intravenous infusion. The construction and implantation of the RSNA electrode involves materials that are easily accessible and relatively inexpensive compared with telemetric nerve recording systems designed for rats and larger animals but which are not presently available for mice. By avoiding anesthesia and restraint, mice with physiological blood pressures in a comfortable, unstressed environment will undoubtedly yield meaningful measures of autonomic control in this species and open many avenues of research using transgenic mouse models.

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**Disclosures**

None.

**References**


**Novelty and Significance**

**What Is New?**

- This is the first description of renal sympathetic nerve recording in conscious, unrestrained mice.

**What Is Relevant?**

- The autonomic nervous system is implicated in the development of hypertension and is a focus of investigation in this field; this method is a valuable and accessible tool for future research in hypertension.

**Summary**

Direct recording of renal nerve activity is possible in conscious, chronically instrumented and unrestrained mice.
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