Video Article

Development of an Algorithm to Perform a Comprehensive Study of Autonomic Dysreflexia in Animals with High Spinal Cord Injury Using a Telemetry Device

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Abstract

Spinal cord injury (SCI) is a debilitating neurological condition characterized by somatic and autonomic dysfunctions. In particular, SCI above the mid-thoracic level can lead to a potentially life-threatening hypertensive condition called autonomic dysreflexia (AD) that is often triggered by noxious or non-noxious somatic or visceral stimuli below the level of injury. One of the most common triggers of AD is the distension of pelvic viscera, such as during bladder and bowel distension or evacuation. This protocol presents a novel pattern recognition algorithm developed for a JAVA platform software to study the fluctuations of cardiovascular parameters as well as the number, severity and duration of spontaneously occurring AD events. The software is able to apply a pattern recognition algorithm on hemodynamic data such as systolic blood pressure (SBP) and heart rate (HR) extracted from telemetry recordings of conscious and unrestrained animals before and after thoracic (T3) complete transection. With this software, hemodynamic parameters and episodes of AD are able to be detected and analyzed with minimal experimenter bias.

Video Link

The video component of this article can be found at https://www.jove.com/video/52809/

Introduction

Autonomic dysreflexia (AD) is a life-threatening emergency in individuals after acute or chronic spinal cord injury (SCI) at cervical or high-thoracic segments and is usually characterized by episodes of persistent hypertension and bradycardia[1]. AD is principally caused by disruption of descending spinal pathways that usually provide input from supraspinal centers to the spinal sympathetic preganglionic neurons that control sympathetic activity and vascular tone[1-4]. AD episodes are characterized by a spike in systolic blood pressure (SBP) up to 300 mmHg and if left untreated may lead to seizures, intracranial hemorrhage, myocardial infarction, and even death[5-8]. A variety of noxious and non-noxious stimuli act as a trigger of AD, including bowel and bladder distension, spasms, pressure sores, urinary bladder catheterization or iatrogenic procedures[9-12].

The temporal development of AD in response to SCI has been investigated in both human[9] and animal models[13,14]. Typically these studies have used an 'induced AD' method (*i.e.*, urodynamics, penile vibrostimulations in humans or colorectal distension in animals) to determine the temporal development of AD. Such an approach is limited by the need for repeated assessments at isolated time-points that may preclude an accurate determination of the temporal development of AD. The use of 24-hr blood pressure monitoring in humans allows serial blood pressure measurements to be made at pre-determined intervals. This technique has recently been employed to monitor spontaneously occurring AD in patients with chronic SCI. In animal models, solid-state pressure transducers are being increasingly used to chronically monitor beat-by-beat arterial blood pressure. Recently, Rabchesvky *et al*. (2012), developed an algorithm that extracted one second averages of mean arterial pressure (MAP) and compared against a moving average threshold[15]. Spontaneous AD events were characterized based on MAP peaks that are 10 mmHg or greater above threshold concurrently with a HR drop of 10 bpm or greater.

Here a novel JAVA software that has a built in AD Detection Algorithm is presented. This algorithm works by detecting pre-determined patterns in arterial blood pressure (ABP) and heart rate (HR) that are indicative of a spontaneously occurring AD event. The user is able to manually adjust all input variables to the software such that the 'detection algorithm' can be easily customized to the specific parameters of interest. The software is also able to dichotomize ABP and HR into a given epoch such that diurnal rhythmicity of hemodynamic parameters can be analyzed[16]. In the present manuscript, a detailed explanation is given of the surgical technique that is used to implant the telemetry devices and conduct the SCI surgery. Examples are also provided with respect to the post-processing capabilities of the AD Detection software and how cardiovascular

function is altered post-SCI. For comparative purposes, the methodology and results obtained from a method of induced AD known as colorectal distension (CRD) is also illustrated.

Protocol

Male Wistar (Hsd: WI Wistar) rats at 7 weeks of age and weighing 300-350 g were used in this experiment. All rats were maintained on a 12 hr light/dark cycle and received standard laboratory rat chow and water ad libitum. All experimental procedures conformed with the guide to the Care and Use of Experimental Animals established by the Canadian Council on Animal Care and granted ethics approval by the University of British Columbia. Surgery and animal care were conducted according to standard procedures in our laboratory (Ramsey *et al.* 2010)[17].

1. Preparation of the Animals: Surgical Procedures

1. **Implantation of the Telemetry Device**
   Note: Protocol was implemented according to the manufacturer's specifications and our previous experience with the implantation of the device: [16]
   1. Pre-treat the animals with enrofloxacin, once a day for 3 days (10 mg/kg, s.c.) pre-operatively.
   2. Remove solid foods from cage 9-13 hr before the surgery. Soft diet nutritional meal replacement may be provided during this period.
   3. Anaesthetize the animals using an induction dose of 4% isoflurane in an induction chamber and a maintenance dose of approximately 1.5% isoflurane (with 1-1.5 L/min Oxygen) using a Bain circuit. Use the toe pinch reflex and corneal reflexes to assess whether animals are at surgical plane of anesthesia. Respiration must be monitored to assess if the depth of anesthesia is too high (*i.e.*, very slow respiration rate and gasping, pale mucus membranes) or too low (*i.e.,* rapid, shallow respirations indicating the animal may not be at a surgical plane of anesthesia). Repeat monitoring of surgical plane of anesthesia approximately every 5 min during the surgery and adjust isoflurane dose as necessary.
      Note: All surgeries are conducted using aseptic technique: specifically, surgeons wear surgical scrubs, cap, mask, and sterile gloves. Open gloving procedure is observed, autoclaved surgical pack containing surgical instruments is opened using sterile technique and the animal is draped before beginning surgery. Surgical tools are tip-sterilized in hot beads between surgeries (for up to five surgeries). Surgical sponges and gauze are autoclaved prior to use. During surgery, animals are kept on a water-circulating blanket maintained at 37 °C.
   4. Administer buprenorphine (0.02 mg/kg; s.c.) immediately before surgery. Further, administer ketoprofen (5 mg/kg; s.c.) prior to surgery to provide multimodal analgesia. Administer bupivacaine (5 mg/kg; s.c.) immediately prior to surgery to provide a local line block. Upon shaving the abdomen, apply alternating swabs of chlorhexidine and 70% ethanol (three times each), followed by povidone iodine for at least 1 min, and remove with 70% ethanol (each time with a newly opened alcohol wipe). Swabbing of the skin is made in concentric fashion beginning at the center of the incision line and circling outward (so as not to contaminate the area by "back/forth" movements). Use sterile gauze swabs and discard between each application. This process is repeated three times before starting animal surgery. Whilst clipped and surgically scrubbed, keep animals on a nose cone connected to a Bain non-rebreathing circuit under approximately 1.5% maintenance dose of isoflurane. Adjust isoflurane level as required to maintain the animal at a surgical plan of anesthesia.
   5. Make a 5 cm long midline abdominal incision cutting through the muscles and peritoneum exposing the intestines.
   6. Retract the intestines (this will expose the descending aorta at the posterior abdominal wall), cover the gut with sterile surgical gauze moistened with 2-3 ml of Ringers solution and keep moist with additional Ringers as often as necessary to prevent tissue desiccation through the procedure.
   7. Blunt dissect around the aorta and separate the aorta from the inferior vena cava utilizing an iris spatulae.
   8. Place ligatures (8-0 monofilament sutures) around the rostral and caudal ends of the outermost adventitial layer of aorta, just distal to the renal artery.
   9. Lift the ligatures briefly occluding blood flow and puncture the aorta at the level of 1-2 mm anterior to the iliac bifurcation with a 25 gauge needle bent at 90° at the tip.
   10. Guide the tip of the catheter of the telemetry device into the aorta using a 20-Gauge curved needle. Advance rostrally to make sure that the tip is just distal to the renal arteries
       1. Fix it using a small amount of tissue adhesive. Remove ligatures and ensure there is no blood flow occlusion due to the catheter or tissue adhesive.
   11. Secure the body of the telemetry device into the abdominal wall using 4-0 silk sutures. Use 4-0 Vicryl and 4-0 Prolene sutures to close the muscle and skin, respectively.

2. **Telemetry Implantation Post-Surgical Care**
   Note: For the first 14 days post-surgery animals should be checked at least 3 times daily, in addition to a detailed monitoring assessment once a day. Assess animals in 7 categories: body weight, physical appearance (pain is assessed based on signs such as increased porphyrin production seen around eyes, nose and front paws, and facial grimace signs), behavior/activity, defecation, skin (including hunching, piloerection, incision healing and seroma), hydration and breathing.
   1. Feed the animals with fruit, assortment of cereals, soft diet nutritional meal replacement, and provide water ad libitum, for 6 days after telemetry device implantation. Animals should have regular solid rodent chow withheld for the first day post operatively. Inject animals with warmed Lactated Ringers solution (5 ml) subcutaneously for the first 3 days after surgery and upon appearance of symptoms of dehydration. Administer Ringers solution (5 ml) as necessary upon assessment of the animals (signs of skin tent, pale ears/mucus membranes) during morning and evening checks.
   2. Administer enrofloxacin (10 mg/kg, s.c.) and ketoprofen (5 mg/kg, s.c.) once daily, for 3 days post-operatively. Administer buprenorphine (0.02 mg/kg, s.c.) during the morning and evening (*i.e.,* every 12 hr) for the following 3 days after surgery. A mid-day dose of buprenorphine (0.02 mg/kg, s.c) may be administered if signs of pain/distress are noted.

3. **Complete Transection of the Spinal Cord**
   Note: Allow animals to recover from telemetry implantation surgery for at least 14 days before T3 complete transection surgery.

1. Pre-treat animals with prophylactic enrofloxacin (10 mg/kg, s.c.) for three days before SCI surgery.
2. Anaesthetize animals under an induction dose of 4% isoflurane as described previously. Further, inject animals with ketamine hydrochloride (70 mg/kg, i.p.) and dexmedetomidine hydrochloride (0.5 mg/kg, i.p.).
   Note: For complete transection surgeries, the vasodilation caused by isoflurane quite often presents problems with hemostasis once the cord is transected. This problem may be prevented by using ketamine/dexmedetomidine cocktail. The animals should be anesthetized for 20-25 min, and reversed using atipamezole (1 mg/kg, s.c.) following the spinal cord transection surgery.
3. Pre-operatively administer subcutaneously buprenorphine (0.02 mg/kg), and ketoprofen (5 mg/kg). Administer bupivacaine (5 mg/kg; s.c.) immediately prior to surgery to provide a local line block. Upon shaving the abdomen, alternating brushes of chlorhexidine and 70% ethanol (three times each), followed by povidone iodine should be applied for at least 1 min, and removed with 70% ethanol (each time with a newly opened alcohol wipe). Brushes are to be made in concentric fashion beginning at the center of the incision line and circling outward (so as not to contaminate the area by "back/forth" movements). Use sterile gauze and discard between each application. Repeat the process three times before starting animal surgery. Whilst clipped and surgically scrubbed, keep animals on a nose cone under approximately 1.5% maintenance dose of isoflurane (adjusted as required to maintain surgical plane of anesthesia). Throughout the duration of the surgery animals are kept on water-circulating blanket maintained at 37 °C.
4. Make a dorsal midline incision, 2 cm in length, in the superficial muscle overlying the C8-T3 vertebrae.
5. Blunt dissect in order to reveal the dura layer.
6. Pierce the dura layer with microscissors or with the tip of a 25 gauge needle.
7. Open the dura at the T2-T3 intervertebral gap and perform a complete transection using microscissors. Open the microscissors but not laterally enough to burst vertebral arteries and veins. In swift motion transect the spinal cord and search for an exaggerated twitch in the animal hind limbs. Confirm a complete transection *via* visual separation of the rostral and caudal spinal cord stumps.
8. After confirmation, place gelfoam between the stumps to achieve hemostasis. Apply sufficient gelfoam to stop bleeding and to separate the stumps of the spinal cord.
9. Use 4-0 Vicryl and 4-0 Prolene sutures to close the muscle and skin, respectively. After SCI surgery, give animals pre-warmed Lactated Ringer's solution (5 ml, s.c. at 30 °C) and allow them to recover in a temperature-controlled environment.

4. **Spinal Cord Transection Post-Surgical Care**
   Note: For the first 14 days post-surgery animals should be checked 3 times daily, in addition to a detailed monitoring assessment once a day. After 14 days detailed monitoring assessment may be repeated every other day. Assess animals in 7 categories: body weight, physical appearance (pain is assessed based on signs such as porphyrin and facial grimace), behavior/activity, defecation, skin (including hunching, piloerection, incision healing and seroma), hydration and breathing. For the first 5-7 days bladders should be checked and expressed at least 3 times per day.
   1. Feed the animals with fruit, assortment of cereals, nutritional soft diet meal replacement, and provide water ad libitum, for 8-14 days after spinal cord transection surgery. Inject animals with warmed Lactated Ringer's solution (5 ml) subcutaneously for the first 3 days after surgery and upon symptoms of dehydration. Administer Ringer's solution (5 ml) as necessary upon assessment of the animals during checks.
      Note: After spinal cord transection, rats exhibit paralysis of the hind limbs, and ambulate using flexion and extension of the forelimbs, which is preserved in this injury model. The rats lack trunk and tail support. To facilitate their movement in the cage, a rubber grid should be placed under rolled oat bedding. This allows rats to grasp the grid with the forepaws, and move readily in the cage to access food and water. The bedding should be changed daily. At day 7 after spinal cord transection, the oat bedding should be replaced by their original wood chip bedding. The rolled oat bedding is used since rats given buprenorphine can develop pica in which they eat bedding and this can cause esophageal impactions. Rolled oats are absorbent impaction of the esophagus with rolled oats has not been observed.
   2. Administer enrofloxacin (10 mg/kg, s.c.) and ketoprofen (5 mg/kg, s.c.) once daily for 3 days post-operatively. Administer buprenorphine (0.02 mg/kg, s.c.) during the morning and evening (*i.e.*, every 12 hr) for the following 3 days after surgery. A mid-day dose of buprenorphine may be administered if signs of pain/distress are noted.

2. Telemetry Monitoring of Hemodynamic Parameters

1. Collect beat-by-beat arterial blood pressure (ABP) and core body temperature every day for 24 hr, pre and post SCI. Sample the arterial blood pressure and core body temperature at 1,000 Hz in 24 hr blocks using the telemetry device.
2. Place a SmartPad under the animal cage for wireless recharging of the transducer and for receiving of digital telemeter signals from the transducers.
   Note: The output voltage is subsequently passed on to a Configurator connected to a computer, which organizes the data flow from each channel. The voltage is converted to continuous arterial blood pressure and temperature recordings. Visualize the sampled data utilizing data acquisition software, such as LabChart.
3. Discard the telemetry data collected during animal monitoring, as well as the 10 min immediately prior to monitoring and 10 min after monitoring.

3. Assessment of Spontaneous Incidences of Autonomic Dysreflexia (AD)

Note: The frequency, severity, and duration of spontaneous AD events were assessed using an algorithm developed for our own novel *AD Detection* JAVA platform software (**Figure 4**). A novel algorithm has been developed to automatically detect spontaneous AD events based on 24 hr SBP and HR telemetry recordings before and after SCI utilizing parameters specified in **Figure 2.**

1. Extract SBP and HR values from raw telemetry data over period of interest using acquisition software.
   Note: Acquisition software detects and determines the value of the SBP peaks from continuous ABP recordings. Heart rate is extrapolated by determining the duration distance between adjacent SBP peaks.

2. Upload a CSV file of the telemetry recordings with interbeat interval in column A, SBP values in column B, MAP values in column C and time of day in column D **(Figure 4A)**.
3. Using the software **(Figure 4B-D)**, specify the relevant physiological HR range *(i.e.,* R to R interval) for the SBP recordings between 180 bpm and 625 bpm. Specify the relevant HR range on the software under the *Heart Rate Minimum* and *Heart Rate Maximum* panels.
4. Create a threshold for SBP and HR through a moving average window of 240 sec. Indicate the window length of the moving average threshold for the analysis in the *AD Duration Threshold* panel.
5. Set a SBP transposed threshold at 20 mmHg above the moving average baseline. Indicate the transposition value in the *Moving Average Threshold Transposition BP* panel.
6. Isolate SBP peak clusters that exceed the transposed threshold with a peak to peak interval less than 2 sec and for a duration of greater than 10 sec. Specify the peak to peak interval using the *Interpeak Interval BP* and the duration interval using the *Peak Cluster Interval BP* panels.
7. Group SBP peak clusters that are within 120 sec of each other.
   Note: Detected potential AD events that are within 120 sec of each other would be grouped as a single event. Specify the maximum duration allowed between consecutive SBP clusters to differentiate separate AD events in the *AD Duration Threshold* panel.
8. Confirm if group of SBP peak clusters are associated with a potential spontaneous AD event by detecting a drop in HR of 40 bpm or greater.
   1. Average 10% of the HR values upon onset of the potential event *(specify this percentage in the upper heart rate drop average range panel).* Average 75% of the heart rate values from the end of the potential event *(specify this percentage in the lower heart rate drop average range panel).*
   2. Subtract the lower heart rate threshold from the higher heart rate threshold, in order to ensure a corresponding drop of 40 bpm or greater. Specify the heart rate drop restriction using the *heart rate drop restriction* panel.
9. Once the panels have been filled, press *OK*. A graphical presentation of the detected AD events are presented, which include the spikes in SBP and associated HR data (**Figure 4C-D**). An output excel file is also generated with the pressor response (mmHg), duration (sec), max systolic blood pressure (mmHg), minimum HR (bpm) and HR drop (bpm) of each detected AD event.

4. Colorectal Distension to Intentionally Elicit AD

Note: The severity of induced AD can be determined through colorectal distension (CRD), a clinically relevant stimulus that mimics the bowel routine[3,18,19].

1. Verify the balloon of a French catheter (straight, 10 French, 3 ml, 35 cm, latex free) is not leaking by inflating it with 2 ml of air.
2. Restrain the animal by wrapping in a towel and allow BP and HR to stabilize for half an hour.
3. Place lubricant on the tip of the catheter. Place a mark on the catheter with a permanent marker, 2cm from the middle of the balloon. The catheter is inserted via the anus into the colon until the mark is just visible at the opening. Secure the catheter to the tail with surgical tape. Re-place the wrapped animal in his home cage placed on the receiver SmartPad matching the implanted transducer inside the animal. Allow the animal's BP to normalize for 10 min.
4. After insertion of the catheter and the associated acclimation period (*i.e.,* 10 min), infuse the balloon with 2 ml of air over 10 sec, allow BP and HR to stabilize. Maintain distension for 1 min. Make sure the tip of the catheter remains inside the rectum. It is important not to over-inflate the balloon (*i.e.,* 3 ml+) in order to avoid rupture of the colon.
   Note: Distension for a duration of 1 min allows appropriate time for the development of the pressor response and the baroreceptor mediated HR drop associated with an induced episode of AD. In addition, this 1 min period also provides sufficient time for normalization of cardiovascular indices.
5. Repeat distension 3 times per trial, repeating trials daily with a minimum interval of 10 min between trials. Once assessment is complete, remove the Foley catheter from the animal.
6. Average beat-by-beat data over 1 sec intervals and report the maximum increase in SBP and maximum decrease in HR over multiple trials.

Representative Results

Using telemetry, arterial blood pressure is sampled at a frequency of 1,000 Hz continuously for 24 hr. An illustrative recording of arterial blood pressure (ABP) using LabChart is shown in **Figure 1B**. The sample ABP was monitored by a solid state pressure sensor inserted into the descending aorta. The novel JAVA platform AD Detection software is able to extract relevant SBP (mmHg) peaks (**Figure 1C**). We may also extract the HR (bpm) from the time interval between adjacent SBP peaks (**Figure 1D**).

SBP and HR extracted from beat by beat ABP sampled at 1,000 Hz are chosen as the input variables for the AD Detection software. The software characterizes spontaneous AD events by an increase in SBP greater than 20 mmHg accompanied by a decrease in HR of 40 bpm or greater, as presented in **Figure 2**. These events are initially identified utilizing a 240 sec SBP moving average baseline transposed vertically 20 mmHg. The AD Detection software ensures the detected AD event is 'real' by checking for a HR drop of 40 bpm or greater with respect to the onset of the AD event. The software detects and characterizes spontaneous AD events from continuous beat by beat, 24 hr SBP and HR telemetry recordings. Along with the time of day and frequency of these AD events, the AD Detection software provides the following tabular information: the max SBP, pressor response, duration of the AD event, min HR and HR drop upon onset of the spontaneous AD event.

The representative graphs of SBP and HR of **Figure 3** present the severity and duration of an induced AD episode during CRD. As the balloon of the catheter is inflated, there is a rapid and persistent increase in SBP, accompanied by pronounced bradycardia. There is a gradual stabilization of the cardiovascular parameters as distension progresses, and normalization of hemodynamic parameters as the pediatric Foley catheter is deflated. After the insertion of the Foley catheter, SBP and HR indices are averaged for 60 sec before inflation to generate a baseline. From the baseline, the severity or pressor response associated with the spike in SBP (mmHg) and drop in HR (bpm) can be determined.

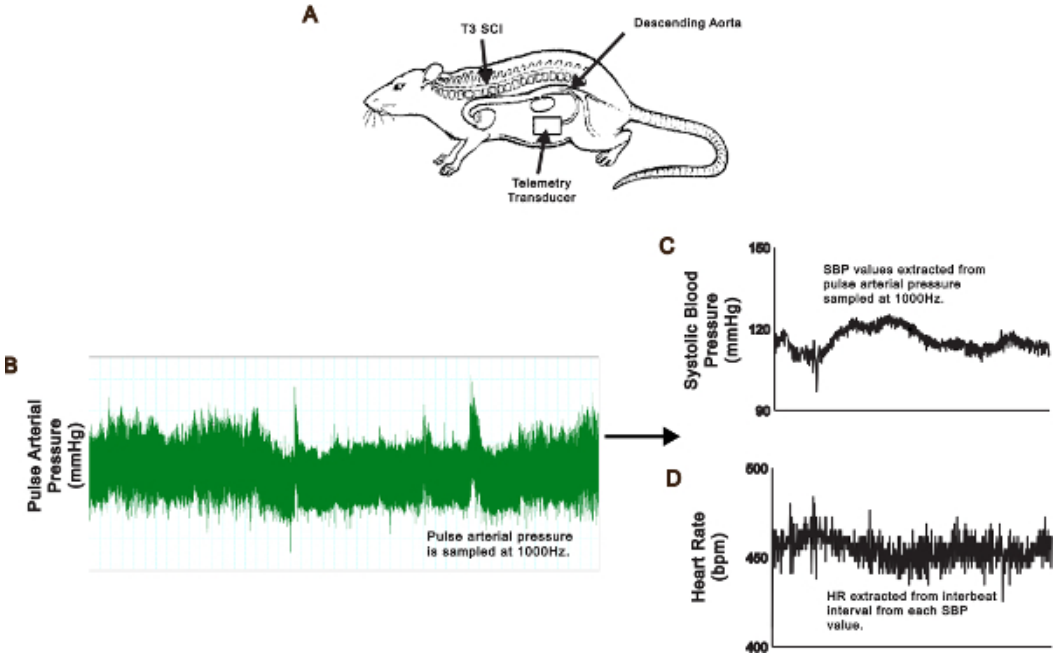

Figure 1. Schematic of Telemetry Device Implantation and Representative Trace of Arterial Blood Pressure (ABP). Schematic illustration of the telemetry transducer implantation with the tip of the catheter directed to the occluded descending aorta and the body of the telemetry device secured to the abdominal wall[16]. Example data of ABP sampled at 1,000 Hz from the telemetry device for a 24 hr period. From this recording, it is possible to extract cardiovascular indices, such as systolic blood pressure (SBP; mmHg; **Figure 1B**) and heart rate (HR; bpm; **Figure 1C**). Please click here to view a larger version of this figure.

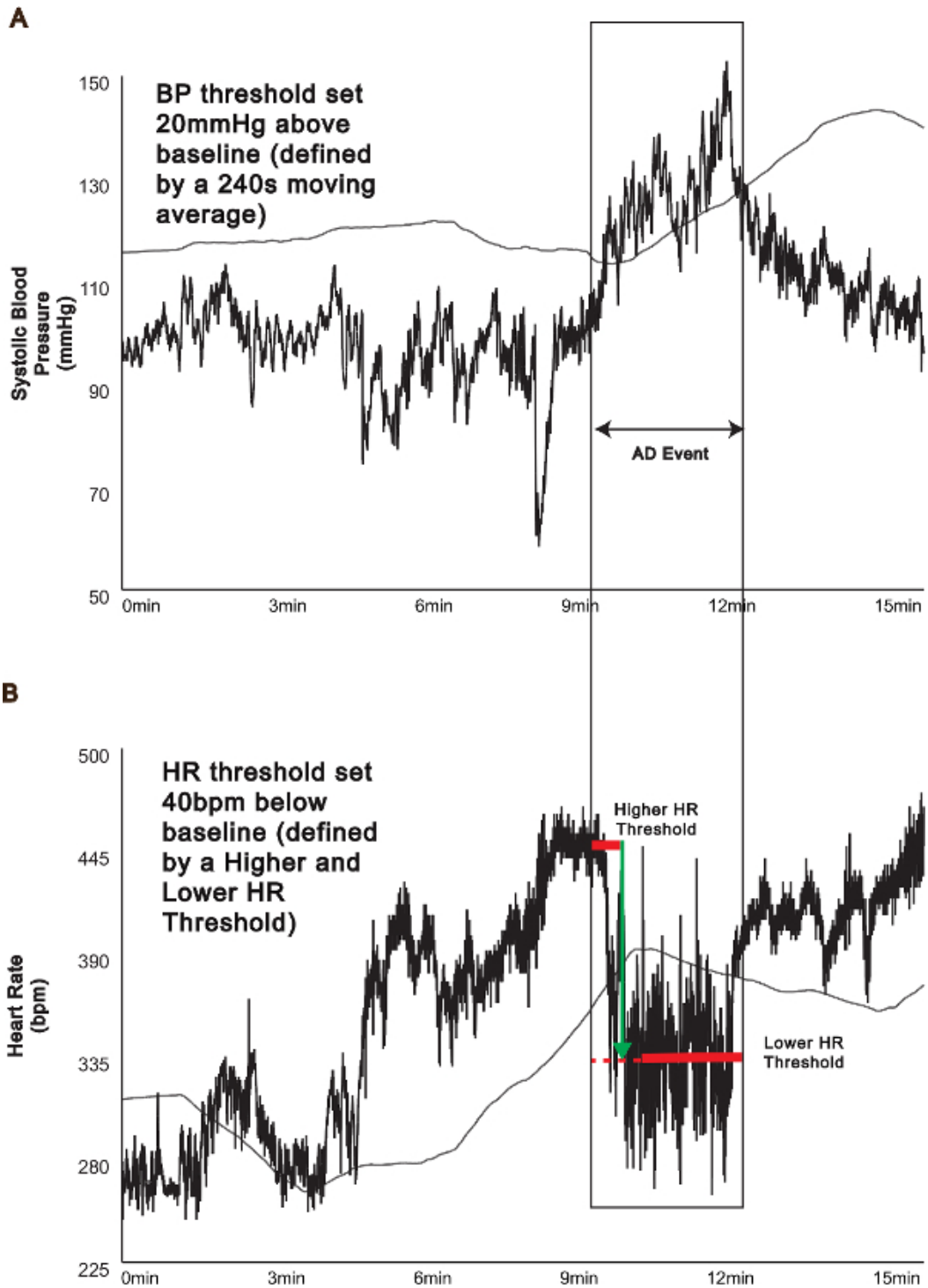

Figure 2. A Spontaneous Episode of Autonomic Dysreflexia (AD) in Spinal cord Injured Animals. The novel JAVA platform software detected spontaneous AD events from 24 hr telemetry recordings of systolic blood pressure (SBP; **Figure 2A**) and heart rate (HR; **Figure 2B**). An increase of 20 mmHg or greater in SBP together with a drop in HR of 40 bpm or greater upon onset of the spike in SBP is considered an AD event. The "upper HR threshold" consists of the mean 10% of the HR values upon onset of the potential event. The "lower HR threshold" consists of the mean 75% of the heart rate values from the end of the potential event. Subtract the "lower HR threshold" from the "higher HR threshold" in order to ensure a corresponding drop of 40 bpm or greater.

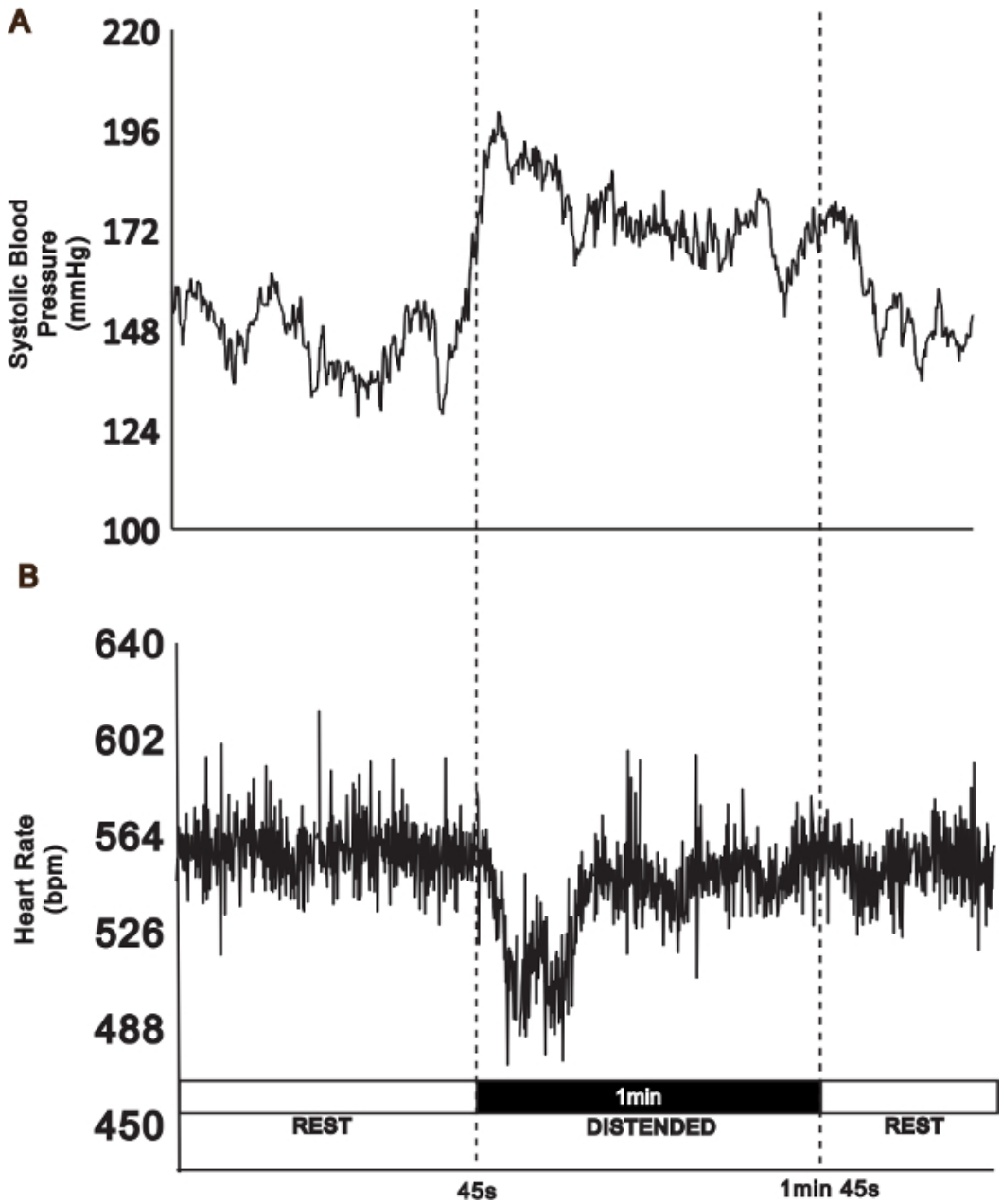

Figure 3. Representative Trace of Induced Autonomic Dysreflexia (AD) by Colorectal Distension (CRD) in Spinal Cord Injured Animals. Upon induction of CRD, there is a sudden and persistent increase in SBP (**Figure 3A**) accompanied by a marked drop in HR (**Figure 3B**).

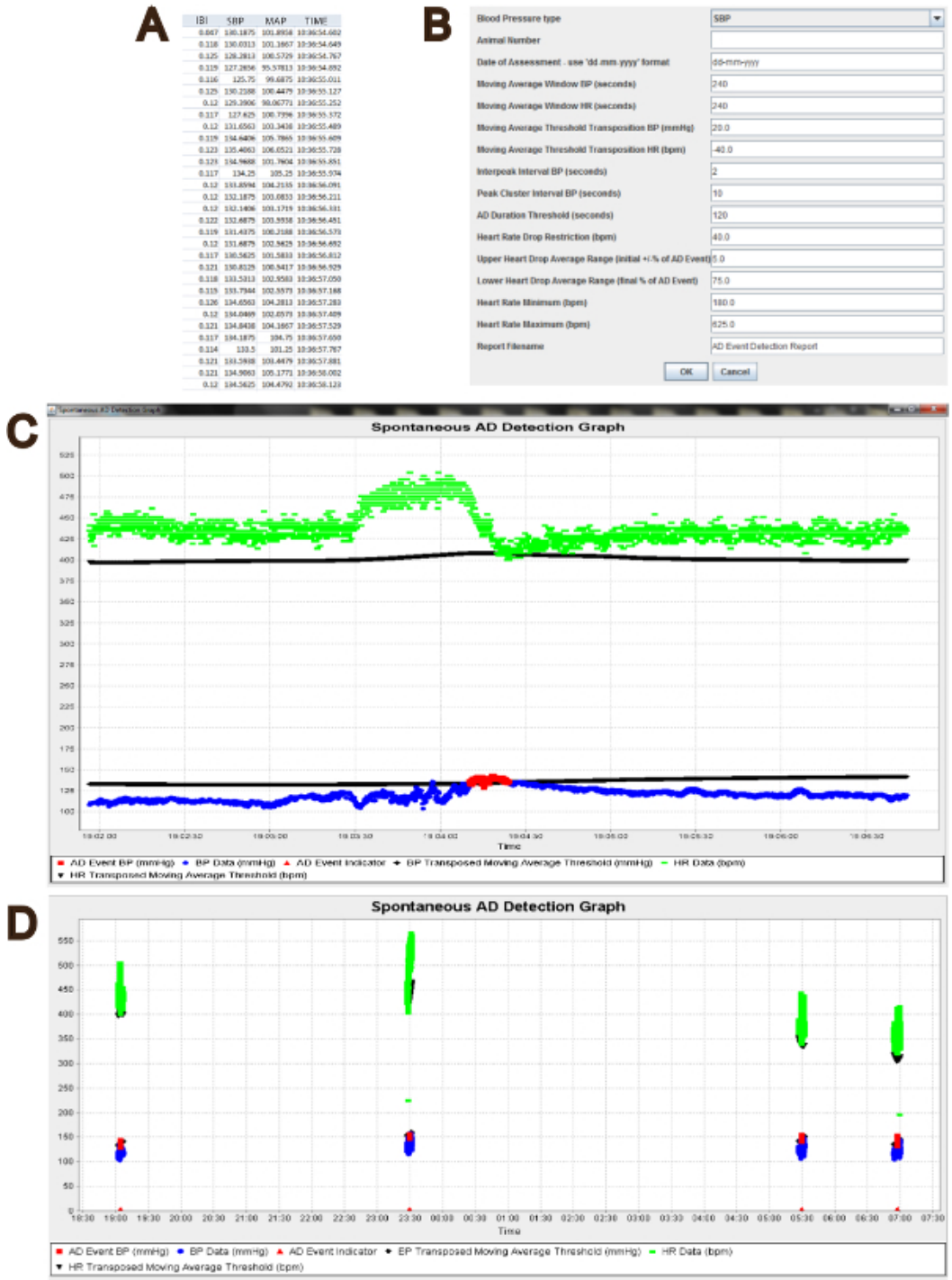

Figure 4. JAVA Platform Spontaneous Autonomic Dysreflexia (AD) Detection Software. A CSV format continuous arterial blood pressure excel file with interbeat interval (IBI), systolic blood pressure (SBP), mean arterial pressure (MAP) and time (**Figure 4A**) is uploaded to the program and the AD detection parameters are specified (**Figure 4B**) as outlined in the protocol. The program presents the temporal phenotype of these spontaneously occurring AD events (**Figure 4C-D**). Please click here to view a larger version of this figure.

Discussion

The protocol describes a detailed implementation of a novel JAVA platform AD Detection software which would be combined with a telemetry device, for a long-term thorough analysis of ABP in SCI-animals (**Figure 1B**). This is the first software that allows for the characterization of ABP patterns to detect spontaneous AD events as they occur sporadically throughout the duration of the day. A well-characterized T3 SCI animal model can illustrate the functional capacity of the software to detect the frequency, pressor response and duration of spontaneous AD. Along

with the detection of spontaneous AD events, the software can analyze oscillations in ABP and discern diurnal variations of hemodynamic parameters.

The novel AD Detection software efficiently, reliably and accurately detected and characterized spontaneous AD events in acute and chronic SCI animals. An AD event is considered to occur upon an increase in SBP of 20 mmHg or greater (**Figure 2A**) and is often associated with pronounced bradycardia[9]. In this particular study, SBP fluctuations were considered a primary indicator for the appearance of a dysreflexic episode, although the software has the ability to also use MAP should the investigator wish. The software has the ability to discern the pronounced bradycardia by detecting the HR drop of a user determined amount upon onset of the AD event **(Figure 2B)**. Rabchevsky *et al*. utilized a characteristic drop of 10 bpm as the threshold upon which a hypertensive event is classified as a spontaneous AD event. This must be questioned, as rodents have a very high resting heart rate; hence, 10 bpm is likely insufficient to define bradycardia. HR drop restrictions may be altered by the user to not only determine drops in HR but also increases in HR depending on the level and completeness of the SCI.

Prior to this software, CRD-induced AD was found to be a robust method of induced AD that is both experimentally feasible and well characterized (**Figure 3A, 3B**)[15,20]. Repetitive induction of AD in rat animal models with high SCI was initially found to mimic the spontaneous and frequent episodes of AD associated with high thoracic SCI[4]. CRD is a potent, noninvasive stimulus for AD in rats with high thoracic SCI[14] which emulates some of the most common causes of AD clinically such as constipation and fecal impaction[3]. CRD-induced AD does not account for the wide variety of afferent stimuli that may also evoke these reflex mediated hypertensive events. Thus CRD-induced AD in conjunction with detection and characterization of spontaneous AD provide the ideal scope in which we can study the temporal phenotype of AD.

Telemetry is a state-of-the-art method for monitoring physiological functions in awake and freely moving animals while minimizing stress-associated artifacts, such as distress, handling and anesthesia[21]. In this case, a solid-state pressure transducer made of a lightweight biosilicone material is used. As opposed to the low pressure response of fluid based catheters, a solid state pressure sensor can monitor subtle changes in cardiovascular parameters. These transducers can sample continuous, beat by beat blood pressure and core body temperature at frequencies up to 2 kHz. Solid state sensors also have the benefit of preventing motion artifacts commonly encountered in fluid based catheters. Though telemetry devices are invasive and costly, it accurately monitors the diurnal rhythm of hemodynamic parameters[15,16,21,22]. The recovery time after implantation is critically important for the survival of the animal, since mechanical obstruction to the blood flow in the abdominal aorta by the implant itself may result in insufficient blood supply to the hind body[15].

Telemetric detection of spontaneous AD, in addition to CRD induced AD, account for the wide spectrum of stimuli associated with the onset of these life threatening episodes. Therefore, detecting and characterizing AD events is critical for considering treatments for SCI patients. There are currently no feasible noninvasive techniques available for humans that allow for chronic, beat by beat, monitoring of hemodynamic parameters. Ambulatory blood pressure monitoring is insufficient due to the low temporal resolution. Animals models are necessary in order to accurately detect and characterize the onset of these spontaneous AD events utilizing the novel AD Detection software. Upon advent of new continuous hemodynamic monitoring technologies, the software may be applied as a vital tool clinically to monitor the onset of these events. The use of telemetry devices in conjunction with the AD Detection software might be a useful future strategy for clinical ambulatory monitoring of acute AD.

Disclosures

The authors have nothing to disclose.

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