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BaroLoop: Using a multichannel cuff electrode and selective stimulation to reduce blood pressure

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***Abstract*— The therapy of refractory hypertension is an increasing problem for health care systems and a frontend in research in both pharmacology and neuroelectronic engineering. Overriding the baroreceptive information of afferent nerve fibers, originating from pressure sensors in the aortic arch, can trigger the baroreflex, a systemic control system that lowers the blood pressure (BP) almost instantaneously. Using a multichannel cuff electrode, wrapped around a rat vagal nerve, we were able to regulate the BP using selective, tripolar stimulation. The tripolar stimulation was sufficiently selective to not trigger any unwanted side effects like bradycardia or bradypnea. The BP was reduced best with charge balanced stimulation amplitudes of 1 mA and pulse duration of 0.3 ms. The stimulation frequency had only a mild influence on the effectiveness of the stimulation and did work best at 40 Hz. We found that the BP took up to five times the stimulation period to recover to the value prior to stimulation.**

I. Introduction

HYPERTENSION is a wide spread disease of civilization. Although most patients can be sufficiently treated with medication, up to 30 % of the patients suffer from therapy resistant hypertension [1]. Overriding the afferent signals from pressure receptors in the aortic arch can trigger the so-called baroreflex regulation. This negative feedback loop lowers the blood pressure (BP) almost instantaneously. Vagus nerve stimulation (VNS) is a well-established and safe neurosurgical treatment of severe epilepsy. There exist several publications on using the aortic depressor nerve (ADN) or the VNS for BP regulation [2,3,4,5]. However, most approaches miss out on appropriate feedback control or the capability to find the appropriate stimulation site for an electrode prior to stimulation.

The vagal nerve contains the pathways for many body functions (Figure 1), making the VNS even more demanding. Insufficiently selective stimulation results in severe side effects like chest and throat pain, cough, voice alteration, nausea, vomiting and even arrhythmia [6]. These side effects are inacceptable for chronically implanted therapeutic systems. The localization of BP relevant fibers is the basic requirement for their selective stimulation. Selective stimulation can be achieved using penetrating electrodes like intrafascicular multichannel electrode [7]. These electrodes deliver access to small groups of fibers but penetrate the perineurium and increase the risk of scar tissue and nerve damage. Cuff electrodes are less selective at the same stimulation thresholds [7] but they allow electronic switching of channels without the need of exact surgical alignment between the electrode and the nerve. For our future BaroLoop™ implant, the signal analysis required for the localization of BP relevant fibers has to be robust, fast and accomplished on an embedded systems with limited computation power (e.g.: MSP430 series, Texas Instruments) [8].

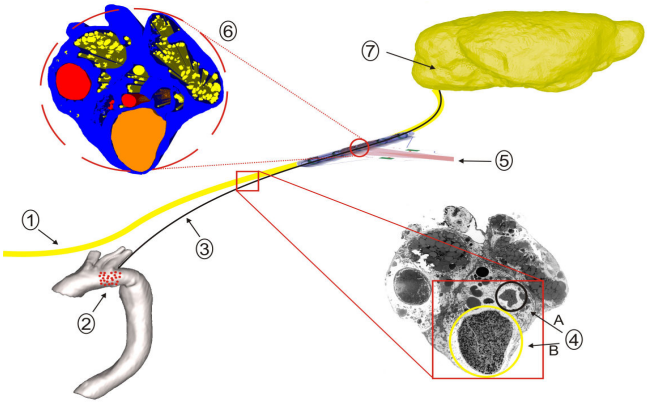

Fig. 1: Schematic of the BaroLoop™ interface in rat. 1. The vagal nerve. 2. The aortic arch with the receptive field of the baroreceptive fibers. 3. The Aortic Depressor Nerve, ADN. 4. Cross-section of the vagal nerve with A) = ADN and B) = N. Vagus. 5. Cuff electrode. 6. Schematic of the vagal nerve at the site of the electrode. Blue = connective tissue, Red = blood vessels, Yellow = fatty tissue, Orange = neuronal tissue. The electrode positions (dashed red line) are relative and not in scale. 7. The rat brain. The first terminal of the baroreceptive fibers is the Nucleus tractus solitarii (NTS) in the brainstem. We thank Dr. von Elverfeld from the Department of Diagnostic Radiology of the University Hospital of Freiburg for the MRI images.

Once baroreceptive fibers were successfully localized using our 24 channel polyimide cuff electrodes, we wanted to learn if stimulation across such channels, found to be co-located with BP relevant fibers, selectively impact the BP without co-stimulating unwanted fibers. We also wanted to learn, which stimulation parameters caused reproducible and long-lasting reduction of the BP.

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II. Materials and Methods

A. Animal Preparation

The data for this study were recorded from five Wistar rats. All proceedings were in full accordance with and approved by the Ethics Committee for Animals Experiments in Baden-Württemberg, Germany. The rats were initially anesthetized with 2-4 % Isoflurane. For analgesia, Carprofen was administered (5 mg/kg bodyweight, s.c.). Anesthesia was maintained with 1-2 % Isoflurane, regulated by the respiration rate. The rats were placed on a regulated heat mat and received saline (3 ml/h, s.c.). The left vagal nerve and the common carotid artery were exposed through a ventral neck incision. The carotid artery was blocked with arterial clamps. A tip catheter (ICP, Codman, 3F) was inserted and fixed in the proximal descending aorta. The cuff electrode was then wrapped around the vagal nerve without any pre-alignments. Afterwards three ECG needle electrodes were inserted subcutaneously in the chest. After initial recording to identify such electrodes that were closest to the baroreceptive fibers, stimulation parameters were tested in arbitrary order to avoid adaptation processes. Stimulation parameters were tested primarily on the identified electrodes and for control purposes also across not identified electrodes. After the experiments the rats were sacrificed and the tissue was harvested for additional histological investigation.

B. Cuff electrode

The polyimide cuff electrode used in the experiments (Figure 1 (6) and 2 A) featured 24 electrodes (1000 nm sputtered Iridium Oxide) combined with a metallization layer of sputtered Platinum (300 nm). The Electrodes were arranged in eight tripoles around the cuff perimeter (45° spacing). Two large ring electrodes facing inside the cuff adjacent to the recording sites and two electrodes facing outside were used as reference or ground, respectively. The cuff total length was 12 mm and the inner diameter was 0.8 mm. The distance between cross sectional electrodes was 2 mm and the total thickness 11 µm [8].

C. Recording and impedance balancing

For the experiments, we used a PZ3 system (Tucker Davis Technology, Florida, USA), which contains low noise pre-amplifiers for the signal conditioning, attached to an RZ2-module. This RZ2 allows digital/analog input/output and holds two digital signal processors (DSPs) to preprocess the signals. The RZ2 was connected to a PC via a PCIe interface card. The PZ3 pre-amplifier was set for recording monopolar signals from each of the 24 electrodes and the 4 reference electrodes at a sample rate of 12207.03 Hz. The noise floor of the amplifiers was 0.9 μV_{RMS}. All input signals were band-pass filtered (Butterworth 2nd order, 20 to 200 Hz). The frequency bands below 20 Hz were rejected because they were continuously present in all tripoles and did not contain any BP-correlated information. Frequency components above 200 Hz were not synchronized or coupled with the BP signal. The BP sensor and the ECG electrodes were also connected to the PZ3 pre-amplifier and were recorded at the same sampling and filter settings as the electrode channels. The post-processing signal analysis on the PC included the calculation of true-tripoles (Figure 2 A and B) of the electrodes, filtering and coherent averaging [8] to detect the baroreceptive activity.

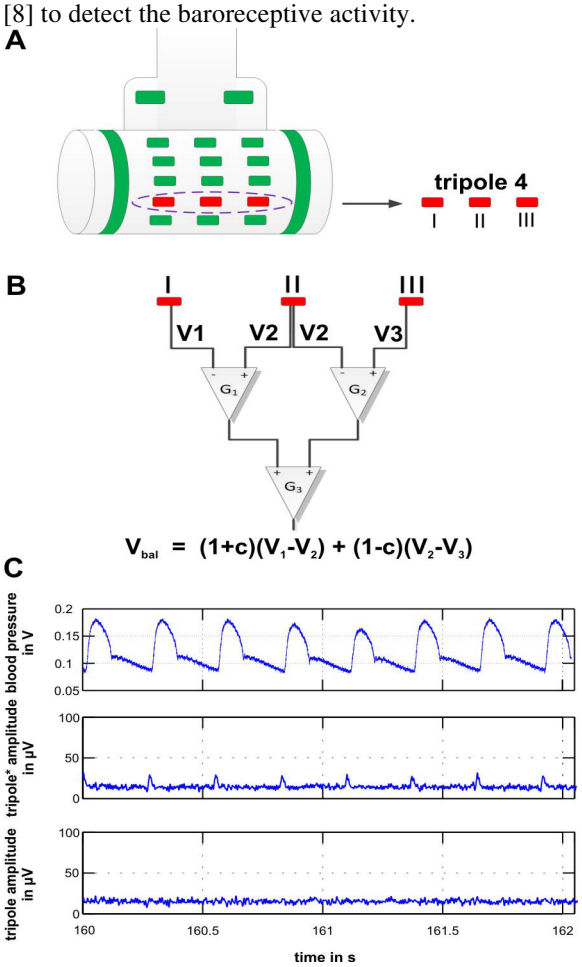

Fig. 2: (A) Schematic of the multichannel cuff electrode used. This array comprises 8 tripoles, 2 counter electrodes facing inside the cuff and two reference electrodes facing outside. (B) Each tripole was amplified in a two-stage process. The first stage allowed impedance balancing, according to equation (1). (C) Recording of the BP (upper track), nerve signals recorded from a tripole with impedance mismatch (middle track) and after balancing (lower track).

D. Stimulation

Current controlled stimulation consisted of biphasic rectangular pulses, which were generated and modified in the RZ2 module and were fed into a custom-made 8-channel voltage-to-current-converter (D/A conversion rate of 24414 Hz, 16 Bit resolution). These pulses were adjusted to be charge-balanced. The standard proceeding was the following: We first located which tripole showed baroreceptive activity after filtering and coherent averaging. We then selected the center electrode of this recording tripole as a cathode against the two large ring electrodes and conducted each combination of stimulation parameter five times in an arbitrary order. All stimulation consisted of 200 pulses.

The following stimulation parameters were tested: repetition rate (30 Hz, 40 Hz and 50 Hz), stimulation amplitude (0.3 mA, 0.5 mA and 1 mA) and pulse width (0.1 ms, 0.3 ms and 0.5 ms). The inter-stimulus-interval was set to be at least 10 seconds. After finishing the 135 combinations of stimulation parameter for the baroreceptive electrode, the same stimulation parameters were tested with the remaining center electrodes.

III. Results

A. *Impedance balancing*

Metal electrodes are subject to impedance change in acute experiments and due to tissue growth even more so in chronic experiments. In order to compensate for this effect we used a two-stage amplification for our true-tripolar recording (Figure 2 B). The true-tripolar configuration allows the elimination of potentials from the recording, which are not located inside of the nerve. Continuous 0.8 and 1 kHz signals found in the recording are intrinsic to the cuff electrode geometry. The electrode dimensions and the spacing between the electrodes determine these frequencies [9]. Similar to the monopolar configuration, unbalanced tripoles contain an ECG artifact (Figure 2 C), which is a useful indicator for impedance mismatches and can be used to minimize this mismatch during chronic implantation. For the detection of baroreceptive fibers, we adjusted the first amplification stage using a compensation factor to eliminate these artifacts:

$$V_{bal} = (1+c) * (V_1 - V_2) + (1-c) * (V_2 - V_3) \quad (1)$$

B. *Identification of baroreceptor regions in the nerve*

After coherent averaging we found in all five experiments one or two tripoles that displayed baroreceptive activity. Stimulation across identified electrodes allowed BP reduction while the remaining electrodes only showed BP decrease at very high stimulation levels (amplitude of 1 mA and pulse width of 0.5 ms) if at all. These results were in accordance with our hypothesis since in rat, the afferent baroreceptive signals from the aortic arch travel across the aortic depressor nerve (ADN), which merges with the vagal nerve (see Figure 1 for anatomy). The ADN either runs closely attached to the vagal nerve or completely merges with it while maintaining its integrity. Overlaying the geometry of the cuff with the anatomical structure of the vagal nerve shows one or two electrodes in close proximity to the unmyelinated fibers of the former ADN (Figure 1 (6)). The stimulation over electrodes in close proximity to baroreceptive fibers vs. electrodes, which are far off, unveils that typical side effects of unselective VNS seem to be located in separate areas of the vagal nerve. The stimulation across an identified electrode (tripole 3) resulted in a long lasting reduction of the BP (Figure 3 B), while neither the heart rate nor the respiration were affected. The same stimulation across another electrode (tripole 6), which did not show any baroreceptive signals during recording and which was not an adjacent neighbor of electrode 3, triggered no reduction of the BP, but resulted in reduction of the heart rate (bradycardia) and in a massive effect on the respiration (bradypnea).

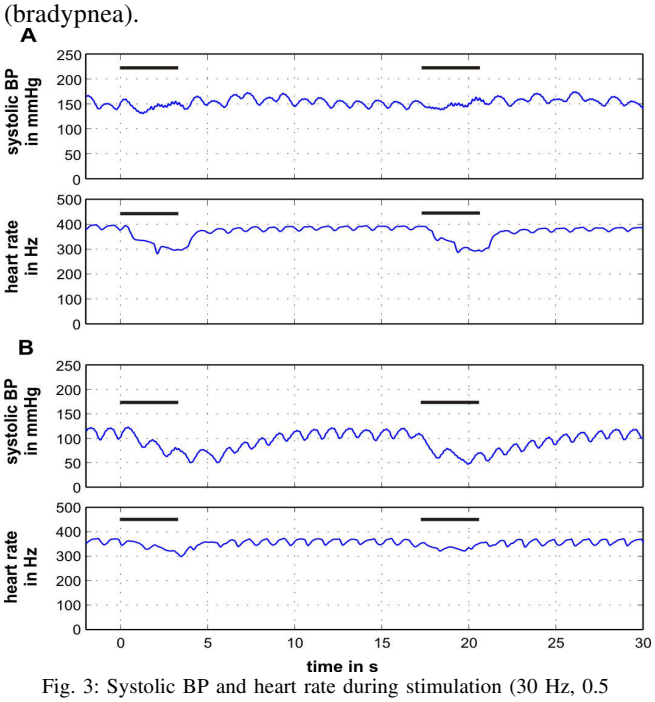

Fig. 3: Systolic BP and heart rate during stimulation (30 Hz, 0.5 mA, 0.3 ms) with electrode 6 (A) and the identified electrode 3 (B). The bars indicate the stimulus time. Note that the respiration of the rat is represented by the oscillation of the BP. That respiration stops during stimulation with unspecific electrode 6.

While only one or two electrodes in a single experiment triggered the baroreflex during stimulation, three to four adjacent electrodes did trigger bradycardia and up to five adjacent electrodes were found to cause bradypnea upon stimulation. These three effects never showed an overlap in terms of the most effective electrode. In order to test our recording and stimulation site, we also rotated the cuff electrode against the vagal nerve. In the consecutively measured localization the baroreceptive electrodes also shifted, in the given case by two positions.

C. *Stimulation parameters*

Since our initial experimental series was limited to five animals, we did not try to run excessive rounds of stimulation parameters to get sufficient data for a detailed rheobase/chronaxie curve. However, based on literature and our own first results, we focused on three different stimulation parameters: the stimulation frequency, the pulse width and the stimulation amplitude. The results for a baroreceptive electrode vs. a non-receptive electrode are illustrated in figure 4. With the identified electrode it was possible to reduce the BP way below safe values of 60 % of pre-stimulus BP. All three stimulation parameters seemed to influence the reduction of the BP. From the three stimulation frequencies chosen, 40 Hz clearly showed the strongest reduction. If the stimulation amplitude was high (1 mA) and pulse width was broad (0.3 or 0.5 ms), i.e.: the charge injection was high, the stimulation frequency became less important. Across all combinations tested, we

found the most suitable and reproducible baroreflex results using stimulation with: 40 Hz frequency, 0.3 ms pulse width and 1 mA current.

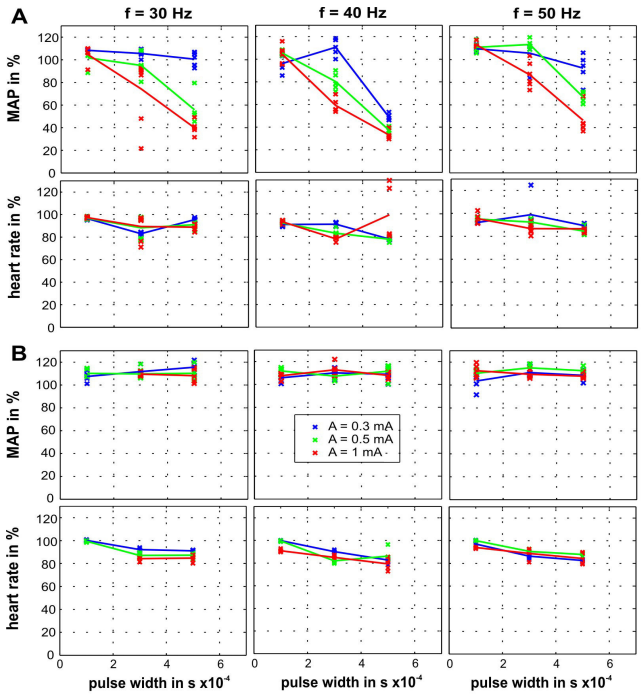

Fig. 4: Response of the mean arterial BP (MAP) and the heart rate as a function of stimulation frequency (columns), pulse width and stimulation amplitude for baroreceptive electrode 3 (A) and not baroreceptive electrode 6 (B). Each stimulus combination was tested five times in arbitrary order.

IV. Discussion

It was shown that the localization of baroreceptive fibers ensures both, a selective stimulation of an almost side effect free baroreflex (for those side effects, which we were able to monitor) and that electrode dislocation can be easily compensated for.

The impedance balancing was useful to detect relative changes of electrode impedance, which typically occurs in an implanted scenario. The corrector factor (c) was an efficient tool to level this mismatch for distortion free recordings. For future chronic trials, we might use these imbalanced values to adjust the charge injection as well.

In all cases, stimulations across the identified electrodes caused a drop of BP with hardly any bradycardia and no bradypnea. The combination of stimulation frequency, stimulation amplitude and pulse width was sufficient to let the BP drop precisely to the wanted 60 %. The stimulation duration remained a constant, but even much shorter stimulations (<1s) caused BP reduction to 60 %. Yet this is an uncharged parameter we will investigate in the future.

We additionally encountered a permanent reduction of the BP pressure after longer sequences of stimulation across the identified electrode. This brought down the systolic BP by some 20 mmHg and is e.g.: the reason why the starting BP in Fig. 3 (A) is way below the one in 3 (B). Another interesting topic we will focus upon in future experiments.

Larger vagal nerve like in sheep and humans will require a higher level of selectivity for stimulation to allow side effect free reduction of BP. In future experiments with sheep we will use the full capability of our electrode (steering currents, pentapolar stimulation, high frequency-(HF) and anodal blocks), which was not necessary in the rat's vagal nerve [10].

V. Conclusion

The function of the BaroLoop™ interface was demonstrated in the vagal nerve of the rat. Localization of baroreceptive fibers in the vagal nerve using a multi-channel cuff electrode and subsequently stimulation across the identified electrode resulted in a side effect free reduction of the BP. With the stimulation parameters amplitude and pulse width it was possible to reproducible lower the BP by a wanted amount.

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