31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Neural Signals in Cortex and Thalamus during Brain Injury from Cardiac Arrest in Rats

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***Abstract*—Previous research has shown that a characteristic burst-suppression (BS) pattern appears in EEG during the early recovery period following cardiac arrest (CA). To study cortical and subcortical neural activity underlying BS, extracellular activity in the parietal cortex and the centromedian nucleus of the thalamus and extradural EEG were recorded in a rodent CA model. Preliminary results show that during the BS, the cortical firing rate is extraordinarily high, and that bursts in EEG correlate to dense spikes in cortical neurons. An unexpected and novel observation is that 1) thalamic activity reappears earlier than cortical activity following CA, and 2) the correlation coefficient of cortical and thalamic activity rises during BS period. These results will help elucidate the mechanism of brain recovery after CA injury.**

I. Introduction

WITH the advent of modern cardiopulmonary resuscitation (CPR) accompanied by defibrillation, the mortality from cardiac arrest (CA) has been reduced. However, neurological outcome after CA remains a major cause for concern with significant long-term neurological sequelae [1]. A better understanding of recovery mechanisms of neural networks after CA provides valuable information to develop clinically applicable diagnostic methods and optimize therapeutic interventions such as hypothermia delivery.

The term burst-suppression (BS) is used to describe the electroencephalography (EEG) pattern characterized by θ and/or δ waves, at times intermixed with faster waves, and intervening periods of relative quiescence [2]. The BS pattern in EEG has been widely reported in deeply anesthesized animals [3], [4], and in subjects resuscitated from CA [5]. Previous research has shown that the characteristic BS pattern observed following CA is a result of dynamic changes in brain perfusion, secondary neuronal injury and electrophysiological recovery [6], [7]. EEG signals result from temporal and spatial summation of postsynaptic potentials from cortical neurons [8], which in turn have a close interaction with thalamic neurons through networks of reciprocal corticothalamic and thalamocortical projections [9]. To obtain a further interpretation of the brain activity that underlies surface EEG signal, neural firing features of thalamus and cortex need to be investigated directly. Most of the *in vivo* studies to explore the mechanisms underlying BS have been done in deeply-anesthetized animals [10]. No studies have directly investigated the neural mechanisms that underlie the BS phenomenon after CA.

In this paper, we study cortical and subcortical neural activity during the early recovery period following CA. Extracellular activity in the parietal cortex and centromedian (CM) thalamic nucleus and extradural EEG were recorded in the rodent CA model. The work focuses on investigating the relationship among bursts in EEG and simultaneously recorded multiunit activity (MUA) for comprehensive understanding of acute neurophysiologic recovery mechanisms after CA.

II. Method

The Animal Care and Use Committee of the Johns Hopkins Medical Institutions approved the experimental protocol used in this study. Adult male Wistar rats were subjected to 7-min asphyxial CA. The CA and resuscitation protocols were performed as previously reported [6].

In brief, anesthesia was induced with 4.5% isoflurane, followed by tracheal intubation. The femoral artery and vein were cannulated for the monitor of mean arterial pressure (MAP) and the administration of fluid and drugs. Multiunit electrodes were then placed into the parietal cortex and CM thalamic nucleus using standard stereotaxic coordinates, followed by placement of epidural screw electrodes for EEG acquisition. After preparation, baseline EEG and extracellular activity were recorded for 15 min. Then global asphyxial CA was induced for 7 min by clamping the tracheal tube and disconnecting the ventilator. CPR was then initiated and return of spontaneous circulation was defined as achievement of spontaneous MAP > 60 mmHg. To minimize the effect of drugs on EEG, no anesthesia was provided post-resuscitation. The core temperature was maintained throughout the experiment at 36.5- 37.5 ℃.

Manuscript received April 7, 2009. This study is funded by NIH grant RO1 HL071568. D. Zhang is supported by the State Scholarship Fund of China Scholarship Council.

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EEG and extracellular activity were recorded simultaneously (baseline: 15 min; CA: 7 min; recovery: 60 min). One channel of bipolar EEG was recorded using screw electrodes (Plastics One, Roanoke, VA). Two electrodes were placed in the left parietal areas (anterior versus posterior). A ground electrode was placed in the right parietal cortex. MUA was recorded in the parietal cortex using a 16-channel microelectrode array (NeuroNexus Technologies, Inc.) and in the CM nucleus using 2x1 tungsten microelectrodes (FHC, Bowdoinham, ME) simultaneously. The CM nucleus was chosen as the target for recording due to its extensive thalamocortical connectivity and its physiological role in arousal, including widespread cortical activation [11].

MUA and EEG were digitalized at sampling frequencies of 6103.5 Hz and 305 Hz by the TDT system (Tucker-Davis Technologies, Alachua, FL), followed by band-pass filtering (0.5-70 Hz for EEG; 300-3000 Hz for MUA). Notch filtering (60 Hz and its harmonics) was performed for all the data. Spike time was detected using the method of Nenadic and Burdick [12]. Firing rate was calculated from the spike count within each 10-sec bin width. Coherence between cortex and thalamus was quantified by correlation coefficient and compared between 10-min baseline (6-15 min) and 10-min BS (46-55 min). The correlation coefficient between two variables X and Y with expected values μ_X and μ_Y and standard deviations σ_X and σ_Y is defined as:

$$\rho_{X,Y} = \frac{\mathrm{cov}(X,Y)}{\sigma_X \sigma_Y} = \frac{E((X-\mu_X)(Y-\mu_Y))}{\sigma_X \sigma_Y}$$

Correlation coefficient was computed for each 10 sec epoch. Wilcoxon rank sum test was used to check the statistical difference in correlation coefficient during different periods.

III. Results

The firing rates of cortical and thalamic neural population before, during, and after CA are shown in Fig. 1. Both the EEG and neural activity became highly suppressed within seconds after CA. Thalamic neural firing reappeared about 7 min after ROSC, followed by the return of cortical firing with singularly high rate (about 14 min after ROSC). At the same time, EEG visibly developed into a BS pattern. BS persisted for about 20 min in this experiment. Then the cortical firing rate gradually decreased, concomitant with the restoration of continuous EEG. Among 16 channels of cortical activity, 14 channels showed similar firing patterns, i.e. normal firing rate during baseline, no firing during CA, dense firing in the early recovery period, and close to normal firing again (refer to the firing rates of cortical channel 1 and 2 in Fig.1). In the other two cortical channels, the neural activities disappeared, possibly due to neuronal cell death caused by CA-induced ischemia. (e.g. cortical channel 0 in Fig. 1). Neural activity in the thalamus did not show obvious "bursts" following CA; instead, the firing rate gradually increased from zero to baseline level during the early recovery period.

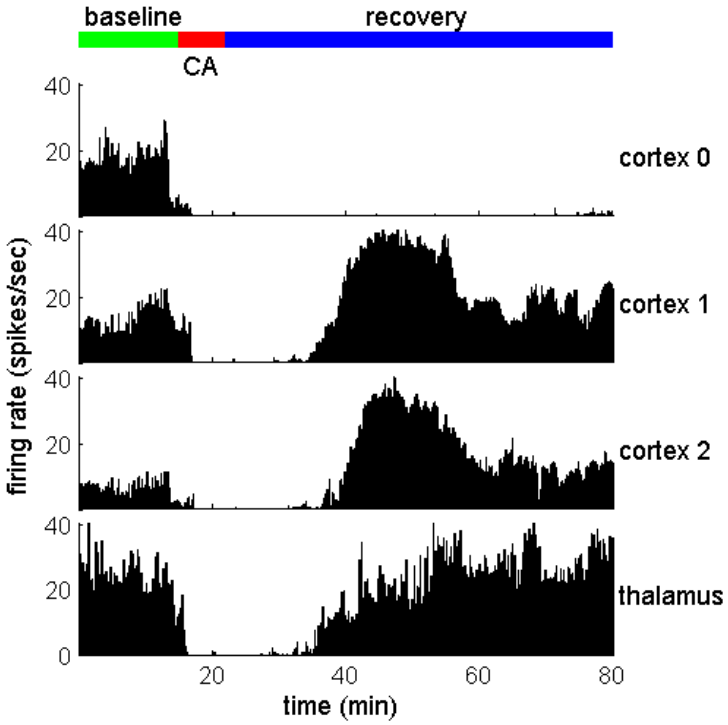

Fig. 1 Firing rates of the neural populations in the cortex and thalamus before, during, and after CA. Baseline: 15 min; CA: 7 min; recovery: 60 min.

Fig. 2 exhibits the burst EEG and 4 channels of MUA in detail. Bursts in EEG correlated with dense spikes in some (not all) of the cortical channels and neuronal firing in all channels largely disappeared during EEG suppression.

Characteristic MUA patterns in cortex and thalamus are selected from different experimental periods and shown in Fig. 3 (cortex 1 to 4: the same channel labels with Fig. 2). Before CA, neurons both in cortex and thalamus fired randomly. However, firing time appeared to be more regular and spikes tended to group together during the early recovery period. Minutes before BS, neural activity in thalamus reappeared while cortical activity remained suppressed. During BS, cortical neurons demonstrated volleys of activity concomitant with some but not all spike bursts in thalamus.

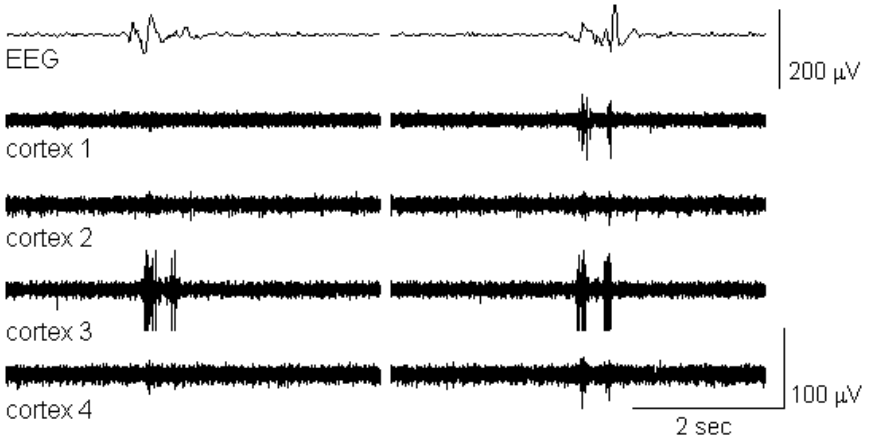

Fig. 2 Characteristic EEG and cortical MUA during BS after CA.

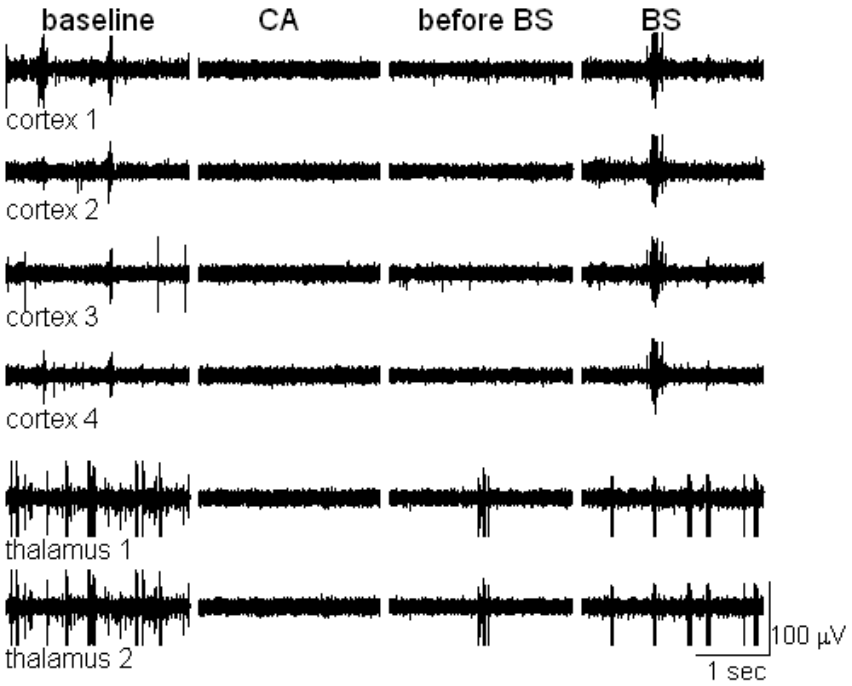

Fig. 3 Characteristic neural activity patterns in cortex and thalamus during baseline, CA, and early recovery period (before BS and during BS). Cortex 1 to 4: the same cortical channels with Fig. 2.

One channel of cortical activity (out of 14 active channels) and one channel of thalamic activity were randomly selected from the recordings. The correlation coefficient between cortex and thalamus was calculated during baseline (6-15 min) and BS (46-55 min) respectively (Fig. 4). The Wilcoxon rank sum test shows that correlation coefficient during BS is higher than that during baseline period ($p << 0.01$).

IV. Discussion

It has been previously demonstrated that reciprocal

thalamocortical and corticothalamic projections exist between the CM nucleus and parietal cortex [13], [14]. With such a neural projection loop, the activities in cortex and CM nucleus exhibit a complex trend (refer to baseline recording in Fig. 3). Compared to the random activity at baseline, neurons in cortex and thalamus display a pathological increase in coherent firing during early recovery after CA (refer to BS activities in Fig. 3). Moreover, we observed that while EEG signal showed periods of bursts corresponding to the activity of cortical neurons, some of the thalamocortical neurons display spike bursts during the periods of electrical silence in the cortex (Fig. 3) [10].

The preliminary study in this paper sets the stage for a more exhaustive investigation of the cellular basis of BS in the brain following CA. We explored the cortical neuronal activity as represented by the BS pattern in EEG along with the thalamic spikes/bursts. This research will help elucidate the mechanism of the origin of the cortical activity at cellular level and help explain the recovery of brain after CA brain injury. Future work will be aimed at determining if causal relationship or coupling exists between different regions of brain. This will involve more extensive measurements of neurons in different areas of brain. More animals and longer recording time will be carried out to support the experimental results obtained and to determine the mechanism of brain injury and recovery under different conditions and different therapies.

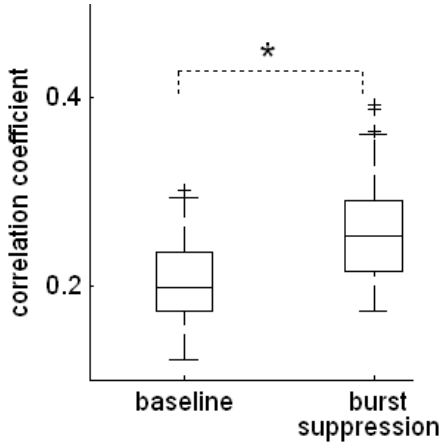

Fig. 4 Correlation coefficient of cortex and thalamus during baseline and BS periods ($p << 0.01$).

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