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Changes in vagus nerve activity associated with ictal tachycardia in pigs

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ABSTRACT

Objective: Ictal tachycardia (IT) is common and may pave the way towards cardiac conditions with high risk potential. However, the mechanisms of IT remain obscure and therefore difficult to control. For example, whereas IT is associated with a sympathetic surge, it is unclear why the IT effects are not opposed by baroreflex cardiac inhibition during seizures. As the vagus nerves (VN) are main mediators for such baroreflexes, this study was performed to investigate the VN activity in IT.
Methods: The present experiments were performed in ten pigs where IT seizures were induced by controlled infusion of pentylenetetrazole. The electrocorticogram was recorded using a cranial electrode, the electrocardiogram (ECG) using surface electrodes and the blood pressure (BP) using a catheter inserted in the right carotid artery. The VN activity was recorded from both nerves using cuff electrodes and further analyzed in correlation with the cortical seizures and the associated heart rate (HR), BP and HR variability (HRV) changes.
Results: The cortical seizures progressed from spike-and-wave (SW) to tonic-clonic (TC) discharges associated with ECG, HR and BP changes proportional with this progression and comparable to the IT effects reported in humans. Those IT effects were accompanied by parasympathetic HRV changes, a 20% VN activation ($p = 0.004$) before the onset of TC seizures, a suppression of this VN activation during the TC episode and a rebound VN activation by 79% (left VN, $p = 0.02$) and 57% (right VN, $p = 0.03$) after the TC offset. Further analysis of an afferent BP-related VN component and a mixed VN component showed normal BP-related afferent input and a suppressed efferent output through both nerves during the TC episode.
Conclusions: This study indicates a suppressed ictal VN activation and a rebound postictal VN activation, which may account for the absence of baroreflexes during seizures and the postictal cardiac inhibition, respectively.

1. Introduction

It is known that seizures are accompanied by autonomic manifestations (Devinsky, 2004; Sevcencu and Struijk, 2010) among which, with a prevalence of up to 100%, ictal tachycardia (IT) appears to be the most common (Sevcencu and Struijk, 2010). Although tachycardia *per se* is rather benign, IT may pave the way to more severe cardiac conditions such as atrial fibrillation, myocardial ischemia and Takotsubo cardiomyopathy (Lemke et al., 2008; Naggar et al., 2014; Nei et al., 2004; Opherk et al., 2002; Tigaran et al., 2003), which may contribute to sudden unexpected death in epilepsy (SUDEP) (Tomson et al., 2008).

Despite this high prevalence of IT and its possible involvement in SUDEP, the mechanisms of the IT developments are not totally understood and therefore difficult to control. For example, whereas IT seems supported by a sympathetic surge triggered by seizures (Benowitz et al., 1986; Lathers et al., 1987; Meierkord et al., 1994), it is not clear why the associated blood pressure (BP) increase is not opposed by a baroreflex cardiac inhibition for as long as seizures last (Rugg-Gunn et al., 2004), or even for more than one minute longer (Mayer et al., 2004). In this regard, studies have shown that the heart rate (HR) in IT typically increases to 120–150 beats per minute (bpm) and can reach values as high as 200 bpm (Sevcencu and Struijk, 2010). In a normal situation, a BP increase consecutive to such HR increase would trigger a baroreflex cardiac inhibition

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through baroreceptor stimulation and parasympathetic activation (Chapleau et al., 1995). Since such responses appear to be delayed even by minutes in IT seizures, one explanation for this dysfunction is that the baroreflex functions perform improperly during such seizures.

Indeed, studies have shown impairment of baroreflex functions in epilepsy patients (Dutsch et al., 2006), but the mechanisms leading to such effects remain unclear. In this regard, it is known that the baroreflex cardiac inhibition is induced by efferent VN cardioinhibitory signals in response to a parasympathetic activation triggered by increased baroreceptor input through afferent VN fibers (Chapleau et al., 1995; Fan et al., 1999; Iriuchijima and Kumada, 1963). As such, a reduction of the VN mediated cardiac inhibition could be due to either a baroreceptor resetting (Dorward et al., 1982), or to a central (Koizumi and Kollai, 1981; Malliani and Montano, 2002; Schwartz et al., 1973) and/or a peripheral (Potter, 1987, 1985; Revington et al., 1990) suppression of cardioinhibitory VN discharges. However, it is not known which of these mechanisms could be involved in IT as a detailed analysis of the VN activity in IT has not been performed yet.

In addition to this mechanistic perspective on the VN activity in IT, learning how the VN activity may change during IT seizures could be important from a therapeutic perspective, too. Thus, our previous studies have shown that the onset of seizures can be early detected based on VN recordings, which may enable on-demand therapies against seizures (Harreby et al., 2011a,b). However, those studies analyzed VN changes associated with ictal bradycardia exclusively (Harreby et al., 2011b) and it is not clear if detectable VN changes occur in IT seizures, too.

Starting from the above considerations, the present study aimed to investigate the VN activity associated with IT seizures. As an experimental model suitable for such work is still missing, the first objective of this study was to develop an animal model of IT seizures. Based on our former experience with a rat model of seizures (Harreby et al., 2011a,b), a previous report on piglet seizures (Terndrup et al., 1994) and a number of preliminary experiments, such a model of IT seizures was developed in pigs subjected to controlled pentylenetetrazole (PTZ) infusion. Using this model, the following objective of this study was to analyze the VN activity during the IT seizures induced in ten animals. This was achieved by analyzing the general VN electroneurography (gVENG) recorded prior and during the IT seizures and more specific components derived from gVENG. Those gVENG-derived components were a phasic component (pVENG) indicative of the above mentioned afferent baroreceptor input through the VN and a tonic component (tVENG) comprising both afferent and efferent contents (Sevcencu et al., 2014).

2. Methods

2.1. Experimental procedures

This study was performed in ten Danish Landrace pigs weighing 45 ± 5 kg. To establish a suitable location for electrocorticogram (ECoG) recording and a proper design for the cuff electrodes used to record the left and right VENGs ($VENG_L$ and $VENG_R$, respectively) the experiments were preceded by a morphometric study in one pig cadaver. In addition, pilot experiments in two pigs were performed to establish a suitable schedule for PTZ infusion. All experimental procedures were carried out under the Danish law in accordance with EU Directive 2010/63/EU.

2.1.1. Surgery

During surgery, the animals were kept under standard sevoflurane anesthesia. The ECoG was recorded using two stainless steel epidural electrodes screwed into the cranium. After exposing the frontal region of the skull, the indifferent electrode was placed 1 cm anterior to the line connecting the supraorbital foramens and the active electrode 2 cm posterior to this line and 1 cm lateral to the interfrontal suture. Our observations in the pig cadaver study corroborated with previous reports (Sauleau et al., 2009), which suggest that the active electrode was placed in a region adjacent to the primary somatosensory cortex and the indifferent electrode in a spongy bone structure.

The electrocardiogram (ECG) was recorded using two surface electrodes to represent lead II, and the arterial blood pressure (BP) was obtained using a catheter inserted in the right carotid artery (Edwards Lifesciences™). To record the VENGs, both VNs were exposed for several centimeters through two lateral neck incisions and a cuff electrode (2.4 mm inner diameter) was placed on each nerve.

As it is known that sevoflurane is epileptogenic (Jaaskelainen et al., 2003) and a ketamine/xylazine combination is typically used in seizure studies (Contreras et al., 1996; Steriade and Contreras, 1995), the anesthesia was switched to IV ketamine/xylazine infusion (20/2 mg/kg/h) after surgery. Under artificial ventilation, the animals were paralyzed with turbocurarine (350 μg/kg, single bolus) and left to stabilize for 15–20 min.

2.1.2. Drug administration

ECoG seizures consisting of spike-and-wave (SW) and tonic-clonic (TC) discharges were induced by PTZ infusion as established in the pilot experiments. After 5 min of baseline recording, the IV infusion of a 200 mg/ml PTZ solution was kept constant at rate of 0.05 ml/kg/min until the total PTZ concentration reached 100 mg/kg (i.e. 10 min), or until the start of TC seizures. In all pigs TC seizures were elicited within a maximum of 14 min. As control experiments, a similar volume of saline was infused in each pig at the same rate prior to PTZ administration. The time interval between the two treatments was at least 15 min after the end of saline administration. All drugs were administrated in the auricular veins of the animals. At the end of the experiments, the animals were euthanized by IV administration of an anesthesia overdose.

2.2. Data acquisition and analysis

All signals were amplified (ECG: 2500–10,000, ECoG: 10,000, VENG: 50,000 and BP: 50,000) and filtered (ECG: 1 Hz–10 kHz, ECoG: 0.1 Hz–10 kHz, VENG: 10 Hz–10 kHz and BP: DC-10 kHz) using AI402 SmartProbes and a CyberAmp 380 amplifier (Axon Instruments, Inc.) and digitized at 16 bits and 50 kHz using a PCI-6251 Data Acquisition Board and BNC-2090 connector (National Instruments®). The data were analyzed off-line in MATLAB® (The MathWorks, Inc.).

The signals were further filtered in MATLAB (ECG: 2–150 Hz, ECoG: 0.1–75 Hz, VENG: 800 Hz–10 kHz, BP: DC-150 Hz), the ECG, ECoG, and BP were down sampled to 1000 Hz, and the ECoG and VENG were squared to obtain the power of the signals. The ECoG power was used to define the cortical energy at the recording site (CoE) as a measure of cortical activation during seizures. The gVENG components pVENG and tVENG were derived as previously described (Harreby et al., 2011a), i.e. by extracting a segment of gVENG, relative to each of the ECG R-peaks, and averaging these segments for all heartbeats occurring within a 10 s moving window to obtain BP-related profiles. These profiles were then averaged into 10 ms bins and their maximum amplitude was defined as the pVENG and their minimum level was defined as the tVENG (Sevcencu et al., 2014). The diastolic BP (dBP) and systolic BP (sBP) were calculated as the minimum and maximum BP, respectively, within each BP pulse. The heart rate (HR) was calculated based on