Published in final edited form as:

Respir Physiol Neurobiol. 2013 June 15; 187(2): 176–182. doi:10.1016/j.resp.2013.03.010.

Fast oscillations during gasping and other non-eupneic respiratory behaviors: Clues to central pattern generation

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Abstract

The mammalian nervous system exhibits fast synchronous oscillations, which are especially prominent in respiratory-related nerve discharges. In the phrenic nerve, they include high- (HFO), medium- (MFO), and low-frequency (LFO) oscillations. Because motoneurons firing at HFO-related frequencies had never been recorded, an epiphenomenological mechanism for their existence had been posited. We have recently recorded phrenic motoneurons firing at HFO-related frequencies in unanesthetized decerebrate rats and showed that they exhibit dynamic coherence with the phrenic nerve, validating synchronous motoneuronal discharge as a mechanism underlying the generation of HFO. In so doing, we have helped validate the conclusions of previous studies by us and other investigators who have used changes in fast respiratory oscillations to make inferences about central respiratory pattern generation. Here, we seek to review changes occurring in fast synchronous oscillations during non-eupneic respiratory behaviors, with special emphasis on gasping, and the inferences that can be drawn from these dynamics regarding respiratory pattern formation.

Keywords

Breathing; Motor synchrony; Gasping; Apneusis

1. Introduction

Fast synchronous oscillations, firing at frequencies well above the primary respiratory rhythm, are manifest in spectra of respiratory-related neural activity (Cohen et al., 1997; Richter et al., 1986; Richter and Ballantyne, 1983; Romaniuk and Bruce, 1991), as well as other neural outputs of the mammalian nervous system. Discharge of the phrenic nerve (PhN), which provides innervation to the diaphragm (the main inspiratory muscle in mammals), contains high- (HFO), medium- (MFO), and low-frequency (LFO) oscillation bands (Bruce et al., 1991; Cohen et al., 1987, 1997; Davies et al., 1985; Dittler and Garten, 1912; Huang et al., 1996; Marchenko et al., 2002; Marchenko and Rogers, 2006a,b; Richardson and Mitchell, 1982; Wyss, 1939). Due in part to differences in intrinsic membrane properties of respiratory motoneurons between different species (Berger, 1979; Dick et al., 1987; Funk and Parkis, 2002; Iscoe et al., 1976; Jodkowski et al., 1987; Purpura and Chatfield, 1952), fast oscillation ranges (Table 1) in rats (Kocsis and Gyimesi-Pelczar, 1997; Marchenko et al., 2002) are twice those (LFO ~ 20–50, MFO ~ 50–100 Hz, HFO ~ 100–200 Hz) observed in cats and rabbits (MFO ~ 20–50 Hz, HFO ~ 50–100 Hz; Ackerson

and Bruce, 1983; Cohen et al., 1997; Schmid et al., 1990) and higher in the *in vivo* rat (Marchenko et al., 2012) than in preparations of the *in situ* juvenile rat (Marchenko and Rogers, 2007; Solomon et al., 2003; St. John and Leiter, 2003) and the *in vitro* neonatal cat (Kato et al., 1996).

Fast respiratory rhythmic output may promote efficiency in muscle contraction. HFO may create a “catchlike effect” in respiratory-related muscles, for example, during the activation of diaphragm motor units, as described by van Lunteren and Sankey (2000). These authors stimulated rat diaphragm muscle strips with 2–4 shocks at 100–200 Hz “bursts” at the onset of 10–50 Hz subtetanic trains. Their results revealed that a high-frequency burst of pulses at the onset of a subtetanic train of stimulation promotes the diaphragm to hold its contractile force at a higher level than expected from the subtetanic trains alone, because of the “catchlike” property of the muscle. This property has been well documented in other skeletal muscles (Burke et al., 1970), and plays an important role in the prevention of muscle fatigue in humans (Binder-Macleod and Barker, 1991).

Originally, HFO and MFO in phrenic spectra had been hypothesized to result from the synchronous firing of phrenic motoneurons (PhMNs) at those frequencies. However, this hypothesis had two principal deficiencies. First, motoneurons firing at HFO-related frequencies had never been recorded (Christakos et al., 1991; Hayashi and Fukuda, 1995; Kong and Berger, 1986; Nail et al., 1972; St. John and Bartlett, 1979). Second, simultaneous recordings of phrenic motoneurons (PhMNs) had never been performed nor related to concurrent phrenic neurogram (population) activity. As a consequence, some suggested that the observation of HFO is epiphenomenological, resulting from the out-of-phase summation of lower-frequency synchronous activity (van Brederode and Berger, 2008). In a recent study (Marchenko et al., 2012), we performed individual PhMN and bilateral PhN recordings in unanesthetized decerebrate rats and used a smoothed pseudo-Wigner Ville distribution to generate time–frequency representations of PhMN–PhN coherence. We recorded PhMNs firing at HFO-related frequencies and demonstrated coherent activity between high-frequency PhMNs and HFO in PhN spectra, validating the hypothesis that fast oscillations are produced by the synchronous firing of motoneurons at those frequencies (Fig. 1).

Changes in fast oscillations have been used by various investigators to indirectly investigate alterations in respiratory central pattern generation, during eupnea (normal breathing; a three-phase respiratory pattern consisting of inspiration [I], post-inspiration [post-I], and late expiration [E2; Richter et al., 1986]) and non-eupneic respiratory behaviors. Behaviors engaging or changing activity patterns in thoracoabdominal and accessory muscles of respiration may either be related or unrelated to ventilation. The former are referred to as respiratory-related behaviors and include eupnea (Richter et al., 1986), apneusis (Lumsden, 1923; Stella, 1938), sighing (Bartlett, 1971), and gasping (St. John and Knuth, 1981). Non-respiratory behaviors include coughing, chewing, swallowing, vocalization, and vomiting and require coordinate changes in breathing to permit execution and prevent aspiration. Changes observed in HFO during different respiratory behaviors have typically involved shifts in spectral frequency, but may also be characterized by changes in spectral power. The recent application of time-frequency analyses to represent spectra and coherence has provided increased sensitivity for detecting subtle changes (Marchenko and Rogers, 2006a,b; Marchenko and Rogers, 2007; Marchenko et al., 2012; Solomon et al., 2003) in fast oscillation dynamics associated with transitions between different respiratory behaviors, which helps inform mechanisms of central respiratory pattern generation and network reorganization during altered modes of breathing (Berger et al., 1978; Cohen et al., 1992; Galán et al., 2010; Leiter and St. John, 2004; Marchenko and Rogers, 2006a, b, 2007;

Nakazawa et al., 2000; Richardson, 1986; Smith and Denny, 1990; St. John and Leiter, 2003).

2. Gasping

2.1. Overview

Gasping carries significant importance in the field of critical care medicine and studying associated spectral dynamics sheds light on respiratory network connectivity and physiology. Gasping may be observed in clinical settings involving severe hypoxemia ($P_{aO_2} < 5\text{--}15$ mmHg; see Guntheroth and Kawabori, 1975) and is characterized by maximal inspiratory efforts peaking in early I and terminating abruptly, evident in PhN activity (PhNA) as decremting short inspiratory duration (T_i) bursts. The gasping response proceeds through four sequential phases (Fewell et al., 2005) after asphyxia or exposure to anoxia or severe hypoxia: (1) hyperpnea, (2) primary apnea, (3) gasping, and (4) terminal (or secondary if autoresuscitation is successful) apnea (Fig. 2). [It should be noted that some authors divide the gasping response into three phases, see Gozal et al., 1996].

Mechanisms underlying gasping generation are at the forefront of a heated debate in the literature (St. John, 1996). Pena (2009) argues for a model whereby gasping occurs through functional reorganization of medullary (*i.e.*, pre-Bötzinger and Bötzinger complexes) and pontine (lateral parabrachial and Kölliker-Fuse nuclei) groups subserving central control of respiration, possibly mediated by hypoxia/anoxia-induced activation of persistent Na⁺ channels in the pre-Bötzinger complex, transiently conferring a pacemaker phenotype to the system. In contrast, other authors (Fung et al., 1997; Ramirez et al., 1998) argue for two fundamentally distinct networks underlying eupnea and gasping, the latter recruited only during conditions of anoxia/severe hypoxia and suggested by St. John (1998) to reside in the rostral medulla apart from the eupnea generator. Investigating changes in fast oscillatory behavior during eupnea, gasping, and intervening transitions may thus provide insights into mechanisms underlying these two distinctive modes of respiration.

2.2. Gasping: in vivo studies

In decerebrate cats, Richardson (1986) showed that eupnea and gasping differ with respect to magnitude of high-frequency peaks (80 ± 13 Hz vs. 120 ± 21 Hz, respectively) within power spectra and inspiratory duration (1.15 ± 0.43 s and 0.55 ± 0.18 s) and on this basis argued for the existence of two central pattern generators (CPGs), one each for eupnea and gasping. It should be noted that the “gasping” described in this study was induced *via* either hypotension (intravenous gallamine or potassium chloride) or hypoxia (fractional inspiration of O₂ not specified) and did not exhibit the decremting pattern that typically characterizes gasping, possibly reflecting “gasping-like” respiratory activity.

The assumption that changes in fast oscillation dynamics during gasping must reflect a fundamental reconfiguration of central respiratory pattern generators is possibly confounded by the hypoxia often used to elicit this respiratory behavior. Hypoxic depolarization may cause increased rate of action potential discharge and account for the positive frequency shifts by the HFO band during the *transition* to gasping. One approach obviating this confounding variable would be to induce gasping without the use of asphyxia, anoxia, or hypoxia. To this end, Tomori et al. (1995) analyzed power spectra in PhN and hypoglossal nerve (XII) of decerebrate cats. The aspiration reflex, which induces “gasping-like” respiratory activity, was elicited *via* mechanical stimulation of the pharynx or electrical stimulation of the glossopharyngeal nerve (IX). Power spectra revealed a shift of the HFO band to higher frequencies during gasping and increased coherence at HFO. The authors interpreted these findings as evidence for suppression of the “eupnea CPG” and activation of the “gasping CPG,” and suggested the existence of two distinct generators mediating these

disparate respiratory behaviors. A major challenge for this interpretation is that these studies showed that HFO coherence is relatively unaffected by eupnea-to-gasping shifts: a completely distinct CPG would have different properties that would at the very least be reflected in coherence changes. Moreover, it should be noted that true gasping may be a respiratory behavior exclusively unique to states of severe oxygen deprivation and non-hypoxic methods of gasping induction (*i.e.*, pharyngeal stimulation [Tomori et al., 1995], hypotension [Richardson, 1986]) may not achieve the medullary hypoxemia necessary for persistent Na⁺ channel activation mediating *true* gasping (Paton et al., 2006; Pena, 2009; Rybak et al., 2004; St. John, 2008). Thus, mechanical pharyngeal stimulation may elicit a respiratory behavior that *resembles* gasping by pattern, but may actually be a distinct respiratory behavior, perhaps a form of “rhythmic sighing,” which typically occurs as sporadic bursts during eupnea (Bartlett, 1971).

In the *in vivo* decerebrate juvenile rat, the high-frequency band shifts toward higher frequencies during the hyperpnea and transition phases of the anoxic response and ultimately *disappears* during terminal gasping, where power becomes distributed in the two lower frequency bands (with 63 and 88 Hz peaks), primarily during the earlier parts of inspiration (Marchenko and Rogers, 2007). Power increases at all bands during the hyperpnea and transition phases of the anoxic response. Additionally, the phrenic start-up component increases in relative intensity with persistence of hypoxia during the gasping response, consistent with the decrementing temporal profile that typifies these bursts. The hypoglossal response to gasping is characterized by a reduction in band power and shifts to lower frequencies. Changes in spectral dynamics during the *initial* phase of the anoxic response may reflect reconfiguration of medullary respiratory circuitry or changes in local processing in response to arterial blood gas and acid–base disturbances. In addition to an orchestrated respiratory response to anoxic stress, direct anoxic depolarization cannot be ruled out as an operant mechanism contributing to the observed changes, as previously discussed. The finding that HFO disappears during gasping *proper* provides stronger evidence than HFO frequency shifts for the hypothesis that multiple CPGs underlie different respiratory behaviors and the disparity in results from other investigators may be explained by differences in species, preparation type, method of gasping induction, and/or selective analysis of terminal gasps *versus* the inclusion of transition bursts (‘pre-gasps’).

In two companion studies, Marchenko and Rogers (2006a) investigated fast oscillatory phenomena in respiratory outputs, as well as dynamic coupling of the same (2006b, *see below*), during the transition from eupnea to gasping in decerebrate adult rats, using novel time–frequency representations of power and coherence. The hyperpneic phase of the transition to gasping was marked by an increase in HFO frequencies, as demonstrated in the decerebrate juvenile rat *in vivo* (Marchenko and Rogers, 2007), as well as replacement of the single MFO peak with two high-power bands within MFO frequency ranges in PhN, both of which exhibited higher maximal frequency peaks than eupneic MFO (Fig. 3). During gasping, there was a disappearance of the HFO band and shifts of the two MFO bands to lower frequencies (Fig. 3). Analogously, XII exhibited loss of HFO during gasping, in addition to spectral shifts to lower frequencies by the remaining bands.

Dynamic changes in coherence (Marchenko and Rogers, 2006b) recapitulate the time–frequency power spectral changes during the transition from eupnea to gasping in decerebrate adult rats (Marchenko and Rogers, 2006a). During eupnea, left–right PhN coherence occurred at HFO and MFO, whereas coherence was observed only at MFO during gasping. Left–right XII coherence consisted of four broad peaks during eupnea which persisted during gasping, but shifted to lower frequencies. Interestingly, PhN–XII coherence increased during the transition from eupnea to gasping, suggesting an important role for coupling among different respiratory motor neuron pools in the response to asphyxia. These

dynamic changes in coupling are reflective of respiratory network reorganization during the eupnea-to-gasping transition, where a common pre-motor generator would drive both hypoglossal and phrenic motor neuron pools. The existence of a neuroanatomical substrate for this coupling is supported by common pre-motor projections from the ventrolateral nucleus tractus solitarius and areas dorsomedial to the nucleus ambiguus in cats (Ono et al., 1994) and bulbospinal neurons in the rat (Lipski et al., 1994).

2.3. Gasping: in situ studies

As described earlier, HFO and MFO frequency bands are lower in the *in situ* arterially-perfused juvenile rat preparation, with HFO in the range 90–110 Hz and MFO in the range 40–50 Hz (Marchenko and Rogers, 2007; Solomon et al., 2003). St. John and Leiter (2003) recorded from PhN in this preparation and showed HFO of approximately 75 Hz during eupnea, which is significantly lower than in the adult rat (Marchenko et al., 2002, 2012). During hyperoxic normocapnia, the peak amplitude of integrated PhNA occurred in late inspiration, which is consistent with eupneic breathing. However, during hypoxic hypercapnia, the peak amplitude of integrated PhNA occurred at the start of inspiration and HFO shifted to higher frequencies, both of which are consistent with gasping. This study, using the temporal profile of integrated PhNA and fast oscillation dynamics, concluded that both distinct respiratory behaviors of eupnea and gasping occur in the *in situ* arterially-perfused juvenile rat, providing evidence in support of the physiological relevance of this preparation for investigating central pattern generation.

Leiter and St. John (2004) recorded PhN, vagus nerve (X), and XII in the *in situ* arterially-perfused rat and showed that inspiratory activities of X and XII precede PhN and X additionally exhibits post-inspiratory discharge during expiration. Importantly, the peak fast oscillation frequencies of PhN, X, and XII during eupnea were equivalent, strongly supporting the idea that a common CPG organizes and couples multiple respiratory-related motor outputs. In addition, XII was shown to possess pre-I activity at frequencies lower than those observed for I. When gasping was induced, pre-I activity disappeared and all nerve activity was purely inspiratory with the peak of integrated activity occurring in early I. Interestingly, the HFO band shifted to higher frequencies in PhN and X, but did not change in XII. Because hypoxia-induced gasping caused respiratory-related nerve activity to shift to a pattern where only inspiratory activity is observed with abolition of pre-I activity in XII and post-inspiratory activity in X, Leiter and St. John argued that gasping is generated by one set of pre-motor neurons while eupnea results from the activity of multiple sets of premotor neurons, presumably organized by a single CPG.

Fast oscillation dynamics in response to anoxia in the *in situ* decerebrate juvenile rat (Marchenko and Rogers, 2007) closely parallel those of age-matched and adult animals *in vivo*. Relative to eupnea, hyperpnea and transition phases are associated with increased power in all spectral bands and increases in left–right PhN HFO coherence. Gasping is marked by loss of power at high frequencies and concentration of the same in the two lower frequency bands over the first half of inspiration. These results are in contradiction to those shown by previous investigators (Leiter and St. John, 2004; St. John and Leiter, 2003) in the same preparation and animal model. These differences may be the consequence of Leiter and St. John's use of hypercapnic hypoxia (8.0–9.5% O₂, 7.5–9.5% CO₂) to induce gasping and the possible inclusion of transition bursts in their analysis *versus* Marchenko and Rogers' use of normocapnic (5% CO₂) anoxia and selective analysis of terminal gasps. Thus, based on the results observed during asphyxia, changes in fast oscillation dynamics from eupnea to hyperpnea and transition phases are consistent with gradual reconfiguration of a common eupnea CPG, but terminal gasping *proper*, typified by loss of HFO, is likely mediated by a CPG distinct from that underlying eupnea.

3. Miscellaneous non-eupneic respiratory behaviors

3.1. Apneusis

Prolonged inspiratory efforts characterize apneusis, which occurs following lesions to the pontine pneumotaxic center (Caille et al., 1981), initially identified by Lumsden (1923) as a region in the rostral half of the pons responsible for inhibiting the caudally related pontine apneustic center, in turn limiting T_i and setting the normal respiratory pattern – ‘pneumotaxy’. Apneustic breathing induced *via* reversible cooling of the rostral pons, mid-pontine transection, and local pneumotaxic center lesioning in anesthetized vagotomized cats all caused shifts of HFO to lower frequencies (Berger et al., 1978). The authors argued that this finding is consistent with a model whereby pontine nuclei are responsible for amplification of the HFO generator’s oscillation frequency, as opposed to recruitment of a novel generator. Further investigation of changes in fast oscillation dynamics during apneusis, complementing the substantially larger body of data collected investigating the same phenomenon during gasping, may serve to elucidate pontomedullary interactions as they relate to respiratory pattern formation.

3.2. Vocalization

Vocalization is associated with changes in several fast oscillation properties. In humans, speaking has been associated with increases in left–right diaphragm EMG HFO coherence, but no analogous change in MFO coherence (Smith and Denny, 1990). During fictive vocalization in decerebrate cats, induced by peri-aqueductal gray matter electrical stimulation, HFO amplitude and frequency increase and a novel left–right coherent expiratory rhythm (50–70 Hz) is generated in recurrent and superior laryngeal nerve power spectra (Nakazawa et al., 2000). The frequency range of this expiratory rhythm and bilateral coherence suggest it may be most accurately designated as expiratory HFO. Whether this represents an activation of a novel “expiratory HFO generator” or reprogramming of phase-dependence within the primary eupnea-related HFO generator is an interesting question that remains to be adequately addressed in the literature.

3.3. Vomiting

Vomiting requires coordination of thoracoabdominal muscle activity to prevent aspiration. Significant changes are observed in fast oscillation dynamics during fictive vomiting in decerebrate cats (Cohen et al., 1992). Power spectra in PhN and lumbar abdominal nerves (AbdN) contain an HFO band at 57–90 Hz that exhibits left–right (PhN–PhN, AbdN–AbdN) and inter-heterologous nerve (PhN–AbdN) coherence during eupnea. Induction of fictive vomiting caused HFO to shift to a higher and broader 84–120 Hz peak, as was observed for gasping, and whereas PhN and AbdN power autospectra were similar upon visual inspection, left–right and PhN–AbdN coherence was completely lost. These results suggest that the locus responsible for *generating* fast oscillations proper may be different than that *coupling* them. If the vomiting and eupnea networks are non-overlapping, the non-coherence of these fast oscillations, despite their HFO-congruous frequency range, would suggest they are not truly HFO, and that the primary HFO generator is actually turned off during vomiting.

4. Conclusion

Fast oscillation dynamics vary in specific ways during respiration and shifts in respiratory modes are paralleled by changes in fast oscillation dynamics. These changes may reflect switching between distinct CPGs or reorganization of a common network functioning to improve harmonization of respiratory-related muscle activity during rapid transitions to different breathing modes. Our recent findings (Marchenko et al., 2012) validating

synchronous motoneuronal discharge as a mechanism underlying fast oscillations help retain many of the inferences made regarding central respiratory pattern generation based on changes in HFO and MFO dynamics during these transitions. In light of the disappearance of HFO during gasping in three different decerebrate rat preparations (adult [Fig. 3] and juvenile *in vivo* and juvenile *in situ*), while the *transition* to gasping may involve reconfiguration of network elements, *gasping proper* is produced by a distinct CPG. Future studies employing simultaneous recordings of individual respiratory pre-motor and motor neurons and whole respiratory-related nerve output during transitions from eupnea to non-eupneic respiratory behaviors may further reveal fundamental properties underlying respiratory network organization.

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Fig. 1. Dynamic PhMN–PhN coherence. (A), (B), (C) and (D) Representative examples of smoothed pseudo Wigner–Ville distribution time–frequency representations of coherence between individual high-frequency PhMNs and ipsilateral PhN. This frequency class of units exhibits highly consistent discharge patterns with large coherence at inspiratory onset and augmenting temporal firing dynamics. *Vertical color bar*, coherence; *x-axis*, normalized inspiration (0–1); *y-axis*, frequency range (Hz).

Fig. 2.

Gasping response. (A) anoxia-induced gasping in the decerebrate juvenile rat *in situ*. (B) asphyxia-induced gasping in the decerebrate juvenile rat *in vivo*. (C) representative bursts characteristic of each phase of the gasping response *in vivo* and *in situ*. Note the ramp-like pattern of eupneic bursts that is diminished in hyperpneic and transition bursts *versus* the decrementing profile that characterizes terminal gasps. Time scale bars are shown in the lower right-hand corner in panels A (40 s), B (20 s), and C (0.4 s). $\int PhN$, integrated phrenic nerve activity; PhN , raw phrenic nerve activity; TP , tracheal pressure (cmH_2O); AP , arterial pressure (mmHg); E , eupnea; H , hyperpnea; T , transition; G , gasping.

Fig. 3.

Fast oscillation dynamics during the eupnea-to-gasping transition. Population-averaged zero-interval subtraction-estimated time–frequency representations of phrenic power spectra during different phases of the asphyxia-induced gasping response in the decerebrate adult rat *in vivo*. *Horizontal color bar*, spectral power in arbitrary units; *x-axis*, normalized inspiration (0–1); *y-axis*, frequency range (Hz). The short epoch after inspiratory offset represents the early post-inspiratory period, into which PhN synchronous oscillations occasionally persist.

Table 1

Respiratory-related nerve oscillation band frequency ranges in unanaesthetized decerebrate adult animals during eupnea.

	LFO (Hz)	MFO (Hz)	HFO (Hz)
Cats	N/A	20–50	50–100
Rats	20–50	50–100	100–200