33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Oscillatory Patterns of Respiration: Consequences for the Stability and Control of Cardiac Electrophysiology

David G. Western, *Member, IEEE*, Ben M. Hanson, Jaswinder Gill, and Peter Taggart

***Abstract*—Periodic breathing patterns known as Central Sleep Apnea (CSA) are often observed in congestive heart failure. This phenomenon is associated with increased risk of sudden cardiac death, but the mechanism for that outcome has not been exposed. Endocardial electrograms were recorded during spontaneous episodes of CSR and PB in patients in conscious and unconscious states. Analysis exposed a regular bidirectional phase-walk in the relationship between respiration and arterial blood pressure. Recently developed signal processing techniques revealed that respiration also modulates cardiac repolarization properties at multiple simultaneous frequencies, and the effect was heterogeneous across measurement sites in both ventricles. These measurements offer unique evidence of the electro-physiological manifestations of these breathing patterns. Analysis of phase relationships suggested a mechanism by which the behavior may predispose patients to cardiac arrhythmias. Such predisposition would be easily measured to direct treatment priorities and improve risk stratification.**

I. Introduction

THE electrical stability and hemodynamic efficiency of each heart beat are dependent on the orchestrated progression of electrical depolarization and repolarization between cardiac muscle cells. Disruption or blockage of this electrical control can occur in various forms, known as arrhythmias. Key factors in the development of serious and fatal ventricular arrhythmias are the temporal and spatial properties of ventricular action potential duration (APD), as has been shown through modeling and simulation [1]-[3] and experimentation in humans [4], [5] and animals [6]-[8].

Central Sleep Apnea (CSA) is a breathing pattern that occurs frequently in Congestive Heart Failure (CHF) and many studies link it with increased mortality [9]-[11]. As the name suggests, the phenomenon most commonly arises during sleep, but occasionally occurs in conscious subjects. CSA is characterized by a gradual oscillation in the tidal volume of respiration between hyperpneas (deep breathing) and hypopneas (shallow breathing) or apneas (no breathing). The oscillations in breathing behaviour (Fig. 1) are accompanied by oscillations in blood pressure, heart rate, and blood oxygen saturation at the same frequency.

The causal relationships among these parameters remain largely undiscovered. However, numerous recent studies have been directed at understanding the nature of these interactions. Respiration is known to modulate cardiac hemodynamics and autonomic input to the heart through a combination of mechanical effects and neural interactions [12]-[14]; Respiratory Sinus Arrhythmia (RSA), in which heart rate oscillates at the breathing frequency, is a familiar non-pathological manifestation of these effects. Changes in blood pressure give insight into autonomic nervous activity, as well as contributing to changes in subsequent autonomic tone via central pathways. This dual-role has been the root of some uncertainty regarding the nature of RSA and whether it emerges from the baroreflex alone or from neural oscillations in the brainstem. Recent debate [15], [16] contributed substantially to the understanding of the phenomenon by citing the relative timings of blood pressure events and changes in heart rate. The present report probes similar uncertainties in the underlying mechanisms of CSA. The phase relationships between oscillations in arterial blood pressure (ABP), respiration, and cardiac electrophysiology were analyzed to gain insight into these mechanisms and their behavior.

This study examines CSA and the associated autonomic perturbations as a potential arrhythmic risk. As a phenomenon that by nature arises spontaneously, invasive studies of CSA are rare. All cases described in this report occurred during a broader study to investigate interactions between cardiac electrophysiology and the central nervous system. The use of endocardial recordings while controlling heart rate eliminates the confounding influence of RSA, offering unique insight into the electrophysiological effects of the syndrome as well as the underlying control mechanisms.

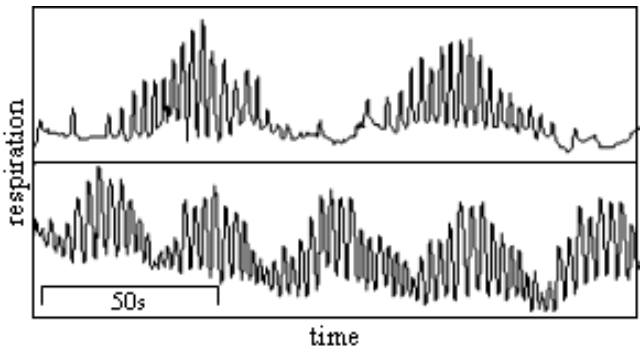

Fig. 1: Examples of CSR (upper panel) and PB (lower panel) from the study. Respiration was measured as chest circumference.

Manuscript received April 15, 2011.

D. G. Western and B. M. Hanson are with the Department of Mechanical Engineering, University College London, London WC1E 7JE, UK, (phone: 0207-679-5702; e-mail: d.western@ucl.ac.uk).

J. Gill is with St. Thomas Hospital, London SE1 7EH, UK.

P. Taggart is with The Neurocardiology Research Unit, University College Hospital, London WC1E 6DB, UK.

II. METHODS

Studies were performed in 16 patients who were undergoing ablation treatment for supraventricular arrhythmias. The study was approved by the Guy's and St Thomas Hospitals Ethics Committee and written informed consent was obtained from all patients. Antiarrhythmic drugs were discontinued for 5 days prior to the study.

Patients were exposed to various mental stimuli, including arithmetic questions, emotive pictures, and controlled breathing exercises, to expose brain-heart interactions. In some cases, drugs were administered intravenously to influence the autonomic nervous system. The drugs used were atropine (to reduce tonic parasympathetic activity) and benzodiazepine (to reduce tonic sympathetic activity).

Unipolar electrograms were recorded using two decapolar electrode catheters. One of these was positioned in a base-to-apex orientation on the postero-inferior endocardial wall of the left ventricle. The second catheter was positioned in a base-to-apex orientation on the anterior septal wall of the right ventricle. A pacing electrode was positioned at the right ventricular apex and used to control heart rate throughout the study. ABP was measured with a catheter transducer (TruWave PX600F, Edwards Lifesciences, Irvine, CA, USA) sited in the femoral artery.

Respiration was measured using a custom-adapted tension sensor fixed to a freely-expandable band placed around the patient's chest/abdomen. The optimum location for each subject was chosen as the site of maximum circumferential strain during normal breathing. Tension in the elastic band was directly proportional to circumference and this output was digitized at a sample frequency of 1200 Hz, synchronized to electrogram and ABP recordings.

As a surrogate measure of APD, Activation-Recovery Intervals (ARIs) were calculated automatically, using the recently developed algorithm described by [4], then subjected to expert review.

The phase relationships between oscillating measures are examined below to investigate possible causal relationships underlying respiration-induced modulation of BP and ARI. The non-sinusoidal nature of the signals prohibits the use of conventional spectral techniques for phase analysis [16]. Instead, a phenomenological approach was used, comparing the timings of the onset of inspiration with the timings of extrema in systolic pressure and any distinct changes in ARI.

III. RESULTS

Instances of CSA were observed in five subjects. Levels of consciousness varied significantly among these subjects. In the most severe case, the subject had recently been awoken from deep but unsedated sleep, and in two other cases the subject was fully awake with no drugs administered. In one case, the subject was conscious but drowsy due to the administration of drugs, and in one case the drugs rendered the subject unconscious. In most cases, the frequency of respiration increased during hyperpnea.

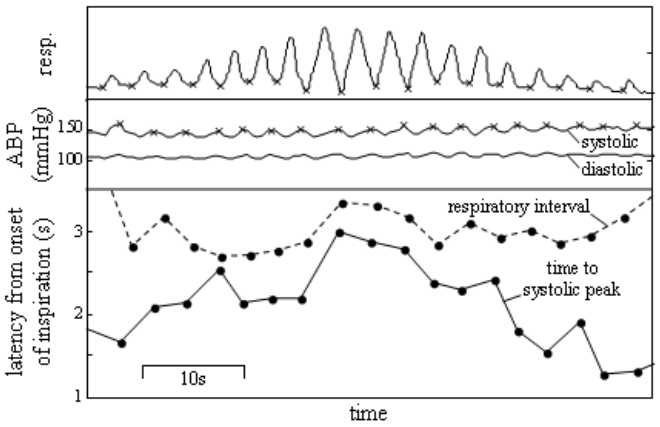

Fig 2: Bidirectional phase-walk in the relationship between respiration and respiratory oscillations in blood pressure during hyperpnea. The top panel shows the respiratory pattern, measured as chest circumference. Crosses mark onset of each inspiration. The middle panel shows the systolic and diastolic blood pressure for each cardiac cycle . Crosses mark peak systolic pressure for each respiratory cycle. The bottom panel shows the relative timings of the events marked by crosses in the first two panels. The solid line shows the latency by which each peak in systolic ABP lags the previous onset of inspiration. The dashed line shows the respiratory interval to the next breath.

In all cases, ABP was found to oscillate at the respiratory frequency, as well as at the lower CSA frequency. It was noted that the latency between onset of inspiration and the subsequent peak in systolic ABP gradually lengthened during the development of each hyperpnea, then shortened, as seen in Fig. 2. Note that the lag between ABP and inspiration increases from less than 2s to more than 3s, then decreases again over the course of the hyperpnea. This pattern differs widely from the changes in respiratory interval, indicating that changes in respiratory cycle length alone are not sufficient to explain the phase shift in ABP. This effect was observed in all subjects. The latencies at the start, peak, and end of hyperpnea were averaged across all hyperpneas for each patient. The mean, maximum, and minimum of these averaged latencies across all patients are summarized in Table 1. Student's t-test confirmed statistical significance for the difference between stages of hyperpnea (middle vs. start: $p<0.02$; middle vs. end: $p<0.01$).

Clear oscillations in ARI were observed at the respiratory frequency in all 5 subjects and at the CSA frequency in 4 subjects. In each case there was substantial heterogeneity in the degree to which these oscillations were expressed, as exemplified in Fig 3. At some sites, only one frequency could be detected. Some sites would express the superposition of both oscillations and others would show no clear pattern. The respiratory oscillations in ARI were not clear enough to reliably establish a phase relationship, but the shortening of ARI generally coincided with inspiration.

	stage of hyperpnea		
	start	**middle**	**end**
mean	1.7s	2.3s	1.5s
maximum	2.3s	2.9s	2.3s
minimum	1.3s	1.8s	0.6s

Table 1: A summary, across all patients, of the amount by which peak systolic ABP lagged onset of inspiration at three stages of CSA cycle.

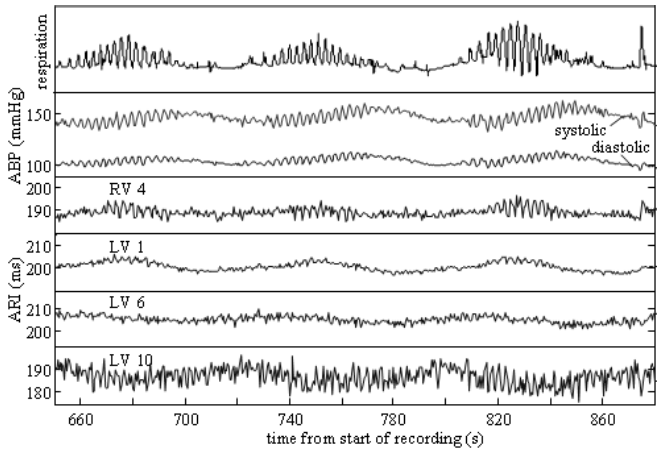

Fig 3: CSA induces oscillations in cardiac electrophysiology at the respiratory frequency (~0.3 Hz here) and the slower CSA frequency (~0.015 Hz) simultaneously, as shown by ARI measurements. The upper panel shows respiration (chest circumference). The second panel shows systolic and diastolic pressure oscillating at both frequencies. The lower four panels show the ARI measurement from a selection of electrodes, chosen to illustrate the heterogeneity with which the oscillations are expressed. These plots are labeled RV or LV to indicate whether the electrodes were positioned in the right or left ventricle, and are marked with a number from 1-10 designating the electrode's position in the apex-base direction. The degree to which each of the two frequencies is expressed in each electrode differs widely. Differences can also be observed in the phase of the slower CSA oscillation, e.g. between LV 10 and LV 1.

IV. Discussion

This study produced the novel observation of heterogeneous, multi-frequency oscillations in ventricular electrophysiology during CSA, indicated by the ARI measurements. Prior research has identified heterogeneous modulation of repolarization properties as a potential cause of fatal arrhythmias [1-3]. The observation of such changes during CSA demands attention when considering the association between CSA and sudden cardiac death.

In agreement with previous studies [17], [18] we have observed characteristic fluctuations in ABP during episodes of CSA. These fluctuations are produced by a variety of oscillatory influences. The expansion of the chest cavity causes decreased intrathoracic pressure while the lungs expand, and thus acts as a mechanical input to ABP [19]. Simultaneously, the phenomenon known as respiratory gating modulates autonomic inputs to the cardiovascular system to influence ABP in the opposite sense [13]; in the present study, pacing eliminates the heart-rate aspect of this mechanism, but it can be assumed that blood-vessel constriction effect persists. Also, any changes in blood pressure are modulated by time-delayed feedback via the baroreflex response, and dynamics at the cellular level are also capable of producing oscillatory behavior. The observed fluctuations in blood pressure are an expected consequence of these mechanisms, which are known but not comprehensively understood. All of the mechanisms described can also be assumed to act as inputs that determine cardiac electrophysiology. Detailed analysis of the precise dynamics of the observable interactions can improve our understanding of the 'gray box' control systems involved, and may help to identify any arrhythmic risk posed by CSA.

The latency between the onset of respiration and the subsequent peak in systolic pressure was found to gradually increase and then decrease during hyperpnea. A similar phenomenon, described as 'bidirectional phase walk', was recently observed in another system of cardiorespiratory autonomic interactions, between arterial pulse and cardiac sympathetic nerve (CSN) discharge during respiratory effort [20]. The reemergence of bidirectional phase-walk in the present report suggests such behavior may be a characteristic of the central oscillators involved in autonomic control.

In generalised dynamic systems analysis, unidirectional phase-walk is conventionally interpreted as evidence of weak coupling between two oscillators. In [20], the bidirectional nature of the changes in phase relationship was taken as evidence of strong coupling of the CSN discharge to a central oscillator whose phase is modulated by respiratory inputs. While this explanation is plausible for our system, we also consider another interpretation: it may be that the apparent change in phase relationship is caused by a shift in influence between two or more follower oscillators, all strongly coupled to the same forcing oscillation but at different phases. This concept can be explained by considering a simple sinusoidal model in which multiple oscillators are driven at the same frequency but with different amplitudes and phases. The observed output y is taken as the superposition of these N oscillations.

$$y = \sum_{n=1}^{N} A_n \sin\left(\omega t + \theta_n\right) \tag{1}$$

The observed output can be expressed as a single sinusoid at the same frequency…

$$y = B\sin\left(\omega t + \phi\right) \tag{2}$$

... with the magnitude and phase as described below.

$$B = \left(\left(\sum_{n=1}^{N} A_n \cos\theta_n\right)^2 + \left(\sum_{n=1}^{N} A_n \sin\theta_n\right)^2 \right)^{1/2} \tag{3}$$

$$\phi = \arctan\left(\sum_{n=1}^{N} A_n \sin\theta_n \Big/ \sum_{n=1}^{N} A_n \cos\theta_n \right) \tag{4}$$

Note that the phase of the output, ϕ, can be modulated by changing the amplitude of any of the driven oscillators, rather than just their phase. Earlier in this discussion, it was explained that various mechanisms driven by respiration, each with a different response time (i.e. phase lag), contribute to the observed ABP. Although the oscillations involved are non-sinusoidal and do not combine as a simple linear sum, this model is useful in illustrating a basic concept: that a shifting phase relationship between the input and output of a system involving multiple parallel branches can be explained by a simple change in the gain of any of

those branches. Each hyperpnea is defined by a crescendo in respiratory effort, and respiratory gating is known to modulate the gain of the baroreflex. It is therefore plausible that the observed change in the phase relationship is caused by a change in the amount of respiratory gating during hyperpnea.

Given that ABP provides a feedback loop to multiple aspects of the cardiovascular control system, the desynchronization between ABP and respiration complicates the range of input scenarios that may be presented to cardiac electrophysiology during CSA. The resultant behaviour therefore becomes less predictable, possibly increasing the chances that multiple inputs will briefly combine to disrupt the normal progression of cardiac electrical excitation and give rise to a fatal arrhythmia. The heterogeneous nature of the observed oscillations in cardiac electrophysiology supports this hypothesis.

V. Limitations

Any study employing unipolar electrograms to measure local electrical activity faces the limitation that the recordings are also influenced by more remote activity. This limitation can be expected to cause some discrepancy between the measured ARI and the local APD. Although such errors are unavoidable, it is certain that some degree of heterogeneous oscillations in the morphology of action potentials occurs at the frequencies observed.

VI. Further Work

Further investigation is required to better characterize the observed desynchronization between ABP and respiration, particularly in the unpaced scenario and with a larger cohort. If a correlation is found between the prevalence of this phenomenon and the occurrence of arrhythmic events, it may afford a simple means of monitoring to improve risk stratification and treatment priorities among CSA patients.

References

[1] D. Noble and Y. Rudy, "Models of cardiac ventricular action potentials: iterative interaction between experiment and simulation," *Phil. Trans. Royal Soc. Lon. Series A: Math.., Phys. Eng. Sci.*, vol. 359, no. 1783, p. 1127 -1142, Jun. 2001.

[2] P. Hunter, P. Kohl, and D. Noble, "Integrative models of the heart: achievements and limitations," *Phil. Trans. Royal Soc. Lon. Series A: Math.., Phys. Eng. Sci*, vol. 359, no. 1783, p. 1049 -1054, Jun. 2001.

[3] R. Clayton and P. Taggart, "Regional differences in APD restitution can initiate wavebreak and re-entry in cardiac tissue: A computational study," *BioMed. Eng. OnLine*, v. 4, no. 1, p. 54, 2005.

[4] D. Western, P. Taggart, and B. Hanson, "Real-time feedback of dynamic cardiac repolarization properties," in *2010 Ann. Intl. Conf. of the IEEE Eng. Med. Biol. Soc.*, pp. 114-117, 2010.

[5] B. Hanson et al., "Interaction of Activation–Repolarization Coupling and Restitution Properties in Humans," *Circulation: Arrhythmia and Electrophysiology*, vol. 2, no. 2, pp. 162 -170, Apr. 2009.

[6] J. Han and G. Moe, "Nonuniform Recovery of Excitability in Ventricular Muscle," *Circ Res*, vol. 14, no. 1, pp. 44-60, Jan. 1964.

[7] J. Wu and D. Zipes, "Mechanisms of initiation of ventricular tachyarrhythmias," in *Cardiac Electrophysiology: From Cell to Bedside*, 4th ed., Saunders, 2004.

[8] W. Gough, R. Mehra, M. Restivo, R. Zeiler, and N. el-Sherif, "Reentrant ventricular arrhythmias in the late myocardial infarction period in the dog. 13. Correlation of activation and refractory maps," *Circ Res*, vol. 57, no. 3, pp. 432-442, Sep. 1985.

[9] P. Hanly and N. Zuberi-Khokhar, "Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure," *Am. J. Respir. Crit. Care Med.*, vol. 153, no. 1, pp. 272-276, Jan. 1996.

[10] P. A. Lanfranchi et al., "Prognostic Value of Nocturnal Cheyne-Stokes Respiration in Chronic Heart Failure," *Circulation*, vol. 99, no. 11, pp. 1435-1440, Mar. 1999.

[11] S. Javaheri, R. Shukla, H. Zeigler, and L. Wexler, "Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure," *J. Am. Coll. Cardiol.*, vol. 49, no. 20, pp. 2028-2034, May. 2007.

[12] J. A. Hirsch and B. Bishop, "Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate," *Am. J. Physiol. - Heart and Circ. Physiol.*, vol. 241, no. 4, pp. H620 -H629, Oct. 1981.

[13] D. L. Eckberg, "The human respiratory gate," *J. Physiol.*, vol. 548, no. 2, pp. 339 -352, Apr. 2003.

[14] D. Baekey, Y. Molkov, J. Paton, I. Rybak, and T. Dick, "Effect of baroreceptor stimulation on the respiratory pattern: insights into respiratory-sympathetic interactions," *Resp. Physiol. & Neurobiol.*, vol. 174, no. 1, pp. 135-145, Nov. 2010.

[15] D. L. Eckberg, "Point:Counterpoint: Respiratory sinus arrhythmia is due to a central mechanism vs. respiratory sinus arrhythmia is due to the baroreflex mechanism," *J Appl Physiol*, vol. 106, no. 5, pp. 1740-1742, May. 2009.

[16] J. M. Karemaker, "Counterpoint: Respiratory sinus arrhythmia is due to the baroreflex mechanism," *J Appl Physiol*, vol. 106, no. 5, pp. 1742-1743, May. 2009.

[17] G. Lorenzi-Filho, H. Dajani, R. Leung, J. Floras, and T. Bradley, "Entrainment of Blood Pressure and Heart Rate Oscillations by Periodic Breathing," *Am. J. Respir. Crit. Care Med.*, vol. 159, no. 4, pp. 1147-1154, Apr. 1999.

[18] R. Leung et al, "Influence of Cheyne-Stokes Respiration on Cardiovascular Oscillations in Heart Failure," *Am. J. Respir. Crit. Care Med.*, vol. 167, no. 11, pp. 1534-1539, Jun. 2003.

[19] M. A. Cohen and J. A. Taylor, "Short-term cardiovascular oscillations in man: measuring and modelling the physiologies," *The Journal of Physiology*, vol. 542, no. 3, pp. 669 -683, 2002.

[20] G. Gebber, M. Das, and S. Barman, "Dynamic changes in baroreceptor-sympathetic coupling during the respiratory cycle," *Brain Research*, vol. 1046, no. 1, pp. 216-223, Jun. 2005.