

Clinical Validation of the ECG-Derived Respiration (EDR) Technique

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Summary

Respiratory signals may be derived from body surface ECGs by measuring fluctuations in the mean cardiac electrical axis which accompany respiration. Two ongoing clinical studies illustrate the value of the ECG-derived respiration (EDR) technique. The first study demonstrates the feasibility of using Holter recordings as a screening test for sleep apnea. In a sample of 9 patients, diagnoses based on the EDR were confirmed by simultaneous polysomnography in all but one case. In the second study, Cheyne-Stokes respiration was observed in a group of patients with severe congestive heart failure. EDR analysis showed that the phenomenon occurred in 8 patients out of 10 who were studied, and that its incidence decreased in 7 of these 8 after chronic oral administration of a positive inotropic agent.

The EDR

We have previously reported on signal processing techniques for deriving respiratory signals from ordinary electrocardiograms [1], based on the well-known observation that the body-surface ECG is influenced by electrode motion relative to the heart and by changes in thoracic electrical impedance as the lungs fill and empty. It is possible to measure a fluctuation in the mean cardiac electrical axis (typically between 1° and 12° peak-to-peak) which is well-correlated with respiration. By interpolating between axis measurements for each normal QRS, a continuous ECG-derived respiration, or EDR, signal is obtained. Alternative methods have been described by Pinciroli et al. [2] and by Pallas-Areny et al. [3] The lead configurations routinely used in ambulatory ECG monitoring are satisfactory for EDR processing, which is therefore applicable to retrospective studies of conventional Holter recordings. We have made use of the EDR technique in two clinical studies at Boston's Beth Israel Hospital (BIH).

Sleep apnea study

Polysomnography is the standard technique for diagnosis of sleep apnea. If it were possible to obtain an accurate diagnosis using the EDR technique applied to Holter recordings, the advantages of this method over polysomnography would be much lower cost and the ability to perform the test in the patient's home. We sought to establish the diagnostic accuracy of an EDR-based test by performing it simultaneously with the standard test and comparing the results. For the present study, Holter recordings were taken on 9 patients referred to the sleep laboratory for possible sleep apnea. Simultaneous polysomnography confirmed sleep apnea in 4 of these patients (group 1), and ruled out sleep apnea in the remaining 5 patients (group 2). An additional 5 Holter recordings (group 3) were drawn from recent referrals to the BIH Arrhythmia Laboratory, and these were selected to match those in groups 1 and 2 in terms of age and cardiac rhythm. The patients in group 3 were considered unlikely to have sleep apnea.

The size of each group and the identity of the group to which each patient belonged were concealed during the initial phases of the study, during which we attempted to identify episodes of sleep apnea on the basis of the EDR, using standard diagnostic criteria for interpretation of conventional respiration signals. Apnea was therefore defined as cessation of breathing for at least 10 seconds. An EDR with an apnea index (the number of apneas per hour) above 5 was considered "suspicious"; otherwise it was considered "normal". When the EDRs for all patients had been examined and classified as either "normal" or "suspicious", the identities of the patients were revealed and the following results were obtained:

	Normal	Suspicious
Group 1 (sleep apnea confirmed)	1	3
Group 2 (sleep apnea ruled out)	5	0
Group 3 (sleep apnea unlikely)	5	0

Figure 1a illustrates the appearance of obstructive apnea in the EDR signal of one of the correctly diagnosed patients in group 1. The misdiagnosed patient in group 1 had obstructive apnea which appeared in most instances as a small amplitude decrease in the EDR (see figure 1b). Modified criteria for diagnosis of obstructive apnea would permit correct classification of this patient without loss of specificity.

It should be noted that the diagnoses of patients in group 3 cannot be verified, since simultaneous conventional respiration monitoring was not available. Overall, these results demonstrate the clinical value of the EDR technique as a screening test for sleep apnea.

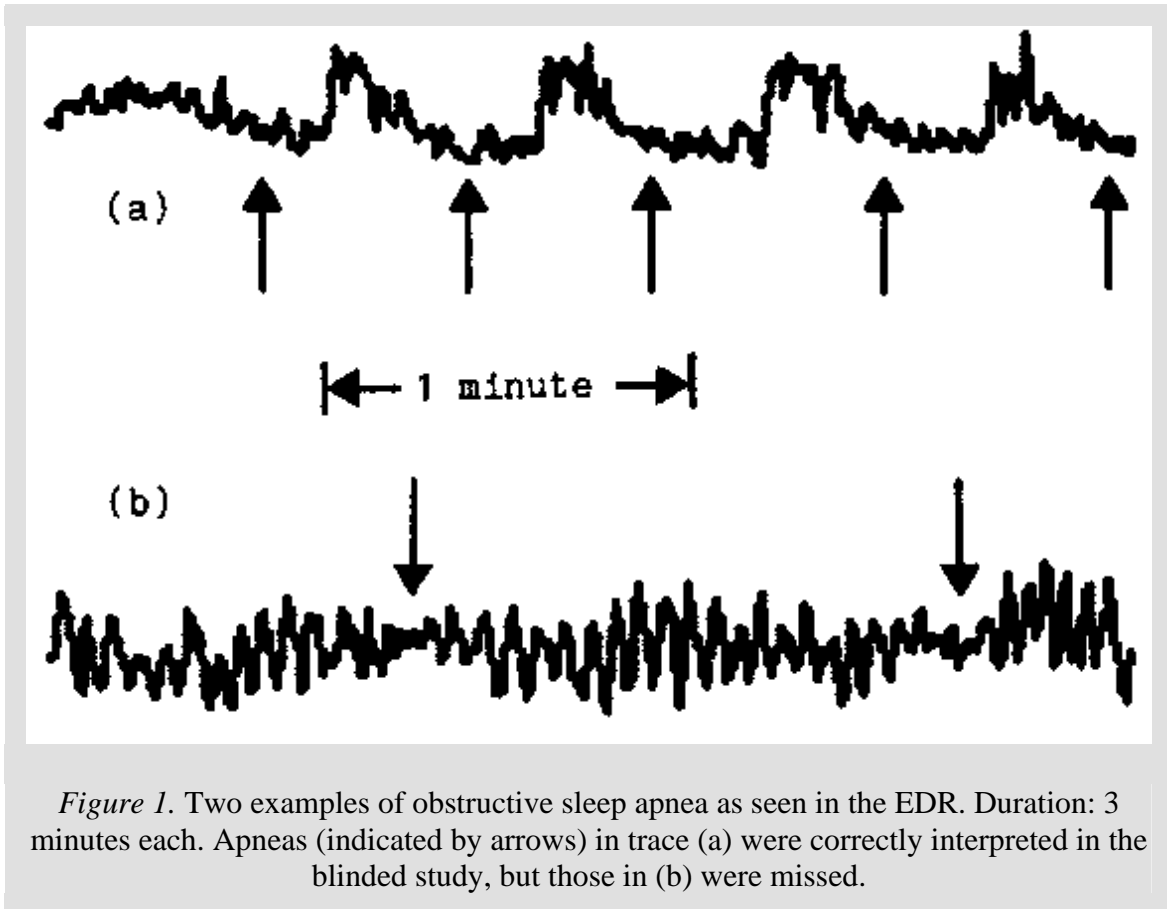


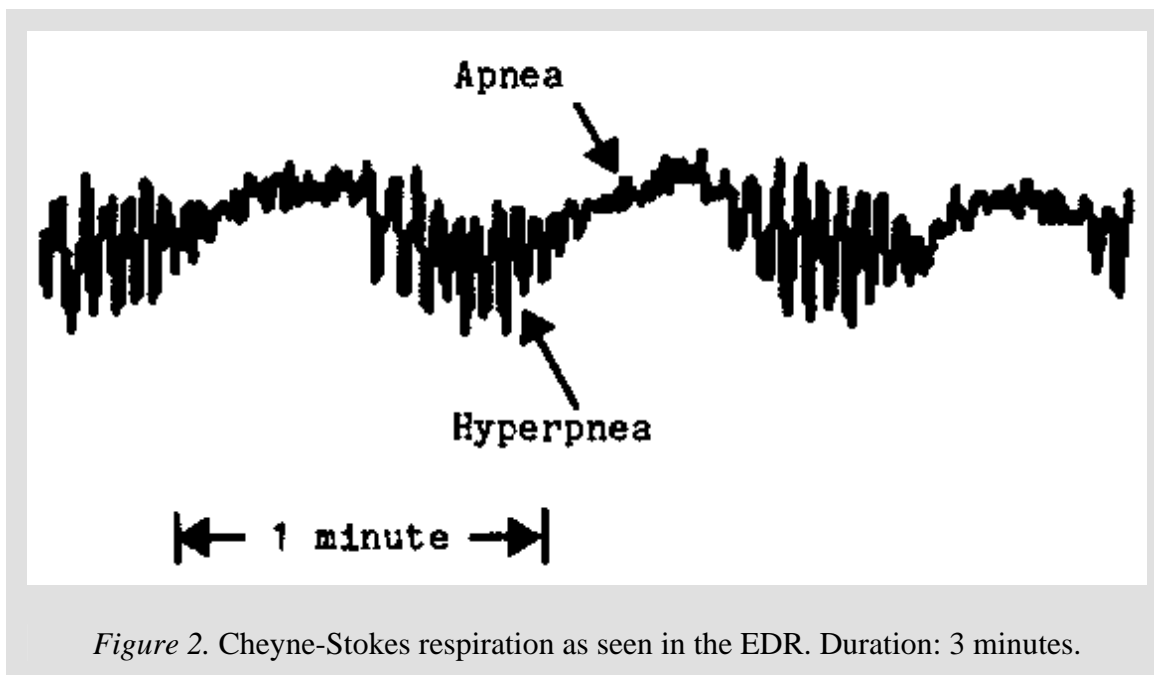
Figure 1. Two examples of obstructive sleep apnea as seen in the EDR. Duration: 3 minutes each. Apneas (indicated by arrows) in trace (a) were correctly interpreted in the blinded study, but those in (b) were missed.

Study of Cheyne-Stokes respiration in CHF

The second study used data from a larger study on the effects of milrinone on patients with severe congestive heart failure (CHF) [4]. Milrinone (Sterling-Winthrop) is an investigational positive inotropic and vasodilating agent. These characteristics may result in increased cardiac output in these patients. From a total of 72 such patients who had received milrinone at BIH, we studied 5 (of 10) who survived for at least 2 years after treatment began, and 5 (of 12) others who died of progressive CHF within 5 months after treatment began, thus selecting representative patients in the population with the best and worst prognoses. For each of the 10 selected patients, we analyzed Holter recordings made shortly before and shortly after administration of milrinone. The total length of the EDR-processed Holter recordings was 389 hours, of which 334 hours (86%) were of adequate signal quality.

Cheyne-Stokes respiration (CSR) is common in CHF, but in most healthy adults it occurs only at high altitude before acclimatization. CSR appears as alternating periods of deep breathing (hyperpnea) which is usually sufficiently rapid to be classified as tachypnea, and shallow breathing (hypopnea) or apnea, which can be detected easily from an EDR

(see figure 2). The hypopneic or apneic phase is typically 50% to 90% as long as the hyperpneic phase, which lasts from 12 to 180 seconds; cycle lengths for CSR vary from 16 to 200 seconds [5]. It has been suggested that prolonged circulation times, due to relatively low cardiac output in CHF patients, delay the feedback between oxygenation of blood in the lungs and stimulation of chemoreceptors in the brainstem, resulting in the oscillations in respiratory amplitude which are characteristic of CSR [6,7].



In unacclimated healthy adults at high altitude, Waggener et al. [8] showed that CSR cycle length varies more between subjects than within individuals, and found that, at 14000 feet (4267 m), the cycle length varied on average by 6% between observations made three weeks apart in the same subject. If a substantially greater change in cycle length is observed without marked changes in environment or level of physical activity, one may conjecture that a change has occurred in the ability of the cardiovascular and respiratory systems to meet the demands imposed upon them. One might therefore predict that in patients for whom milrinone is effective, more rapid circulation should result in a decrease in the amount of CSR, and a decrease in its cycle length.

In the present study, the prevalence of CSR was 80%. This high rate reflects the severe degree of underlying cardiac decompensation in the patients studied. Only two patients (one survivor and one non-survivor) did not experience CSR. Altogether, 102 episodes of CSR were observed. The mean duration of CSR episodes was 18.35 minutes (range 1.6 minutes to 2.5 hours). The mean CSR cycle length was 73 seconds (range 20 to 180 seconds). CSR accounted for 14.0% of the total analyzable EDR; in the 14 recordings in which CSR was observed, the amount ranged from a low of 0.5% (in one of the survivors after treatment) to a high of 47.3% (in one of the non-survivors before treatment).

In 7 of the 8 patients who experienced CSR, we noted decreases in the number of episodes per hour after chronic administration of milrinone; CSR was observed in the eighth patient only after treatment (see figure 3). The total duration of CSR episodes decreased in 2 survivors and 3 non-survivors, but increased in another survivor and another non-survivor. Marked decreases in cycle length (greater than 40%) were observed in 2 survivors; in another survivor there was a moderate increase (15%), and no cycle length changes were noted in the remainder of the patients studied. These results suggest that milrinone is effective in reducing susceptibility to CSR, but without implications for the clinical outcome,

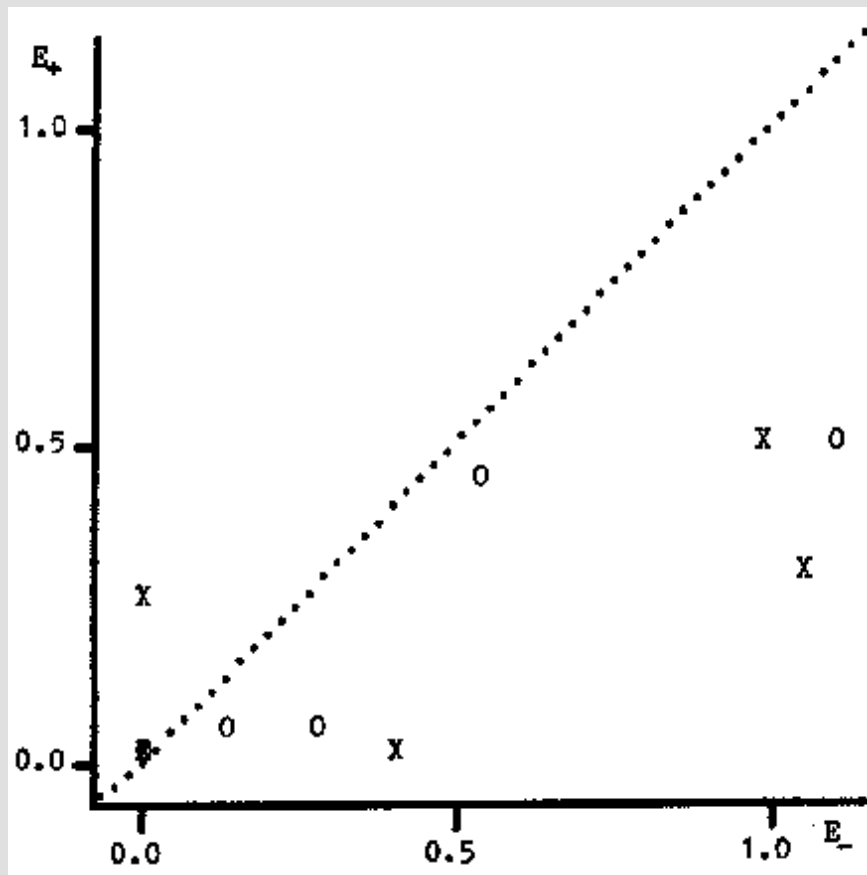


Figure 3. CSR episodes/hour before (E-) and after (E+) administration of milrinone. Survivors are plotted as "0", and non-survivors as "X". Note that E+ is lower than E- for 7 of the 8 patients for whom CSR was observed.

We observed in these data that cyclic variations in heart rate often accompany CSR, as reported previously by Goldberger et al. [9] In CHF, such variations are often the only significant fluctuations in heart rate, since respiratory sinus arrhythmia (RSA) is of very low amplitude or entirely absent. The striking differences between heart rate spectra of a healthy individual and a CHF patient are reflected in their EDR spectra (see figure 4). Using information provided by the EDR, it is possible to describe a heart rate spectrum

concisely with a three-component model, comprised of narrowband RSA- and CSR-related terms superimposed on a wideband $1/f$ term which may reflect the responsiveness of the cardiovascular system to the variety of environmental stimuli which impinge upon it. Since the locations of the CSR and RSA components can be determined from the EDR spectrum, the EDR facilitates fitting this model to a heart rate spectrum and reduces the uncertainty in the fit. The effect of CHF on the heart rate spectrum may be characterized as a loss of both the $1/f$ and RSA components (reflecting the inability of the system, already driven to its limits, to meet demands on it), coincident with the appearance from time to time of a CSR-related component which is absent in the normal spectrum.

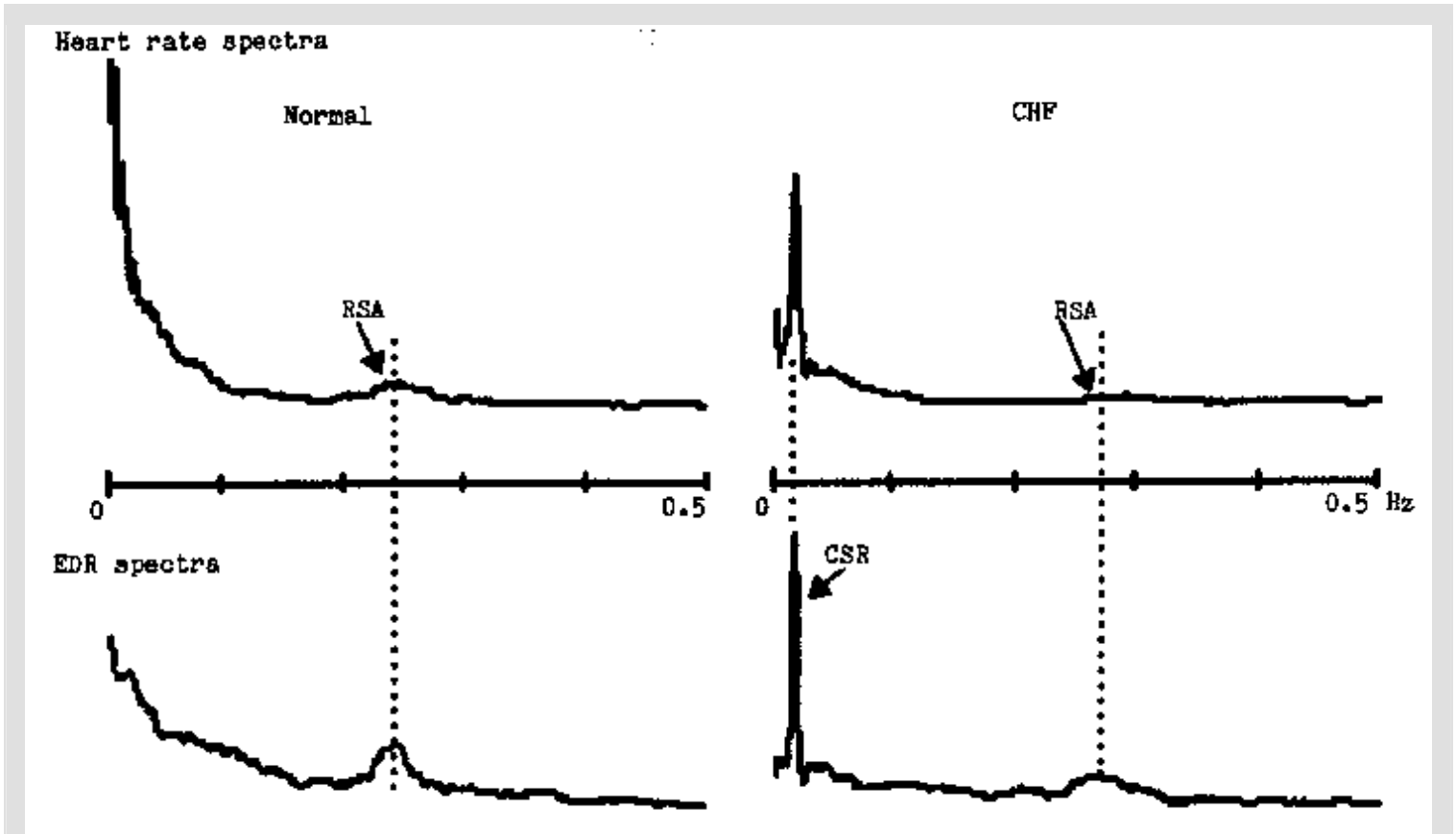


Figure 4. Heart rate and EDR spectra. The spectra at left are from a healthy female, age 61; those at right are from a female with CHF, age 59. Note the substantial $1/f$ component and the respiratory sinus arrhythmia (RSA) at 0.24 Hz in the heart rate spectrum at upper left, matching the dominant peak in the EDR spectrum at lower left. By contrast, in the heart rate spectrum at upper right, the $1/f$ and RSA components are diminished, and the dominant feature is a peak at 0.018 Hz, matching the Cheyne-Stokes peak in the EDR spectrum at lower right.

Conclusions

The clinical studies described above suggest the value of the EDR technique. In the first study, the EDR provided a new approach to monitoring respiration for the purpose of

identifying sleep apnea. This approach is far less costly than studies requiring fully equipped sleep laboratories, and may be more suitable for serial studies and evaluation of therapy as well as for screening. In the second study, the EDR increased the utility of an existing Holter database: it is now possible to use a library of ECG recordings as a library of respiration recordings. Without the EDR technique, we would have no information about respiratory patterns in these patients, because no conventional long-term respiration recordings were made. Having obtained this information using the EDR, we have been able to study the dynamics of Cheyne-Stokes breathing in CHF and its relationship to heart rate variability.

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