Journal of Cancer Research and Experimental Oncology Vol. 2(5), pp. 60-71, December 2010
Available online http://www.academicjournals.org/JCREO
ISSN 2141-2243 ©2010 Academic Journals

Full Length Research Paper

Investigation of breathing maneuvers using free breathing and video biofeedback techniques during radiation therapy treatment for non small cell lung cancer patients

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Accepted 20 October, 2010

The goal of radiation therapy treatment increases as the breathing motion decreases, which then will lead to desirable and accurate conformal dose distributions for mobile lung cancer tumor. Twelve healthy volunteers of age ranges between 18-63 years, (5 females and 7 males) were randomly selected for the study in the breathing training methods using free breathing and video biofeedback breathing. The free breathing patterns of subjects without external intervention varied considerably. It can also be observed that the patterns of breathing for each subject were not always consistent or constant with respect to time. However, video biofeedback generally controlled the variability in the breathing amplitude. The subjects, on average, breathed deeper than normal (that is, compared with free breathing) and the video mentoring helped them to maintain constant amplitude better than the free breathing method. It is concluded that the video biofeedback appeared to be generally superior to the free breathing technique in terms of its better control over the reproducibility of the baselines, amplitudes and frequencies and might produce stable breathing patterns for patients during the radiation therapy treatments of non small cell lung cancer.

Key words: Non small cell lung cancer, respiratory motions, 3D-conformal radiotherapy, intensity-modulated radiation therapy, breathing monitoring, free breathing, video biofeedback.

INTRODUCTION

Lung cancer remains the most common cancer-related cause of death and nearly 1.5 million new cases diagnosed worldwide every year (Spiro et al., 2010). The use of 3D-conformal radiotherapy (3DCRT) and intensity-modulated radiation therapy (IMRT) in conjunction with higher doses of fractionated radiotherapy with dose between 60 and 70 Gy may improve local disease control and overall survival (Beltran et al., 2010), however, this goal is limited by increasing toxicity and pneumonitis due to irradiation of surrounding organs and healthy tissues of the lungs (Hope et al., 2004). Reducing the margin around the gross tumor volume (GTV) and the planning tumor volume (PTV) has the potential to limit radiation toxicity (Beltran et al., 2010; Grills et al., 2003) but increases the risk of geographical miss especially when the respiratory motion involved (Low et al., 2003; Essapen, 2001; Chen et al., 2001). Various breathing monitoring and control techniques had been clinically implanted and used, all intended to focus in increasing the prescribed dose to the tumor and minimizing radiation to surrounding normal tissue and organs at risk (OAR).

Inter-fraction motion occurs because the patient is typically treated using multiple treatment fractions; for each fraction, the patient has to be positioned on the treatment couch in a manner which reproduces the planned alignment with the radiation beam. Despite efforts to deliver the treatment as accurately as possible, the position will nevertheless differ from day to day. To date, in most radiation therapy departments, problems

associated with inter-fraction movement have been controlled as much as possible, through the use either of patient immobilization devices- such as the alpha-cradle (Bentel et al., 1997), the body foam-bag and the T-bar (Halperin et al., 1999) - or of portal films or electronic portal imaging devices and image-guided radiotherapy, which are designed to reduce setup errors and to increase the accuracy of everyday treatments (Mah et al., 2000). The most popular techniques that used are fluoroscopic imaging of the tumor motion (Chen et al., 2001), tracking internal markers (Shirato et al., 2001; Sharp et al., 2004; Vedam et al., 2003; Vedam et al., 2001; Kini et al., 2003), monitoring external markers (Kealle, 2006; Rosenzweig et al., 2000), breath holding (Mah et al., 2000) or active breathing control (Wong et al., 1999) and using a spirometer to monitor lung tidal volume changes (Zhang et al., 2004). The aim of this study was to develop a breathing training method that is feasible for radiotherapy patients with non-small cell lung cancer. This method could be used in a clinical routine session without additional measurements or treatment time.

MATERIALS AND METHODS

Subjects and treatments

Twelve subjects (5 males and 7 females) were randomly selected for this study to investigate the proper breathing patterns to produce a stable breathing which will then limit the chest wall movement. The investigation involved two breathing training methods, one is free breathing where the subject breathes normally without any intervention and the second one is video biofeedback breathing. All of the subjects have adequate pulmonary function, were well mentally oriented, able to follow the procedure, able to discuss and sign the consent forms, and experienced no problems with vision or hearing. The subjects had a full introductory session concerning the device Figure 1, the purpose of the study, and had the right to ask any questions. Any subject with significant cough, pain, or anxiety or with abdominal or shallow breathing patterns was excluded from this study. Three of the volunteers had been smokers for a long time, while the remaining participants were non-smokers. The chest expansion was measured by a custom-made belt and strain gauge, which then simply buckled around the subject's chest.

The tension in the belt, which could initially be easily adjusted for the subject's comfort, would vary in response to the subject's breathing, increasing with inhalation, and decreasing with exhalation. In order to ensure that the sensor was placed in the correct position, a short measurement (of less than four minutes) was carried out prior to the actual data collection session. This allowed the sensor, belt position and tightness, monitor location and lighting to be optimally adjusted; all of these parameters were then fixed for each of the data collection/training sessions for that particular subject. During the measurement, subjects were placed in supine position with their arms in the sides, since the literature suggests that breathing is predominantly controlled abdominally when the arms are placed above the head (Kima et al., 2007). Inhalation and exhalation breathing phases and breathing time were recorded. For every subject, the position of every maximum inhalation and every maximum exhalation was determined for 4-min measurement period. The subject was not shown any breathing data, nor was the subject 'trained' in any way during this initial setup phase. The period, amplitude and phase patterns of the subject's breathing were recorded for four minutes in two different breathing training protocols and then the e data was exported directly to Excel spreadsheets. The sensor readings are illustrated in Figure 3, as time-series plots, condensed into one page to permit a quick visual comparison. Each plot has a common time scale from 0 to 240 s, and a common sensor reading scale from 0 to 300. Figure 4 shows the variance in C, α, ω, and φ with respect to subjects and Figure 5 shows variance in C, α, ω, and φ with respect to time whereas Figures 6 shows comparison of mean amplitudes with respect to time and treatment and Figure 7 shows comparison of mean frequencies with respect to time and treatment. It can be observed at a glance from Figures 3-6 that the breathing patterns varied considerably both within and between the subjects and treatments. It can also be observed that the patterns of breathing for each subject were not always consistent or constant with respect to time.

Free-breathing session

The first session of breathing training was the free-breathing. The subject was asked to lie on a clinical bed for a total of four minutes, and the buildup belt was placed between the lower part of the chest and the upper part of the abdomen. The subject was asked to breathe normally, with no requirement to perform any particular kind of breathing. During this time, the breathing cycle was recorded via the sensor to the laptop computer. No images, sounds or any other biofeedback were presented to the subject. After the recording of the breathing cycles, which lasted for four minutes, the subject was told the session had concluded and was asked to rest prior to the next collection session. During this time, the time-averaged natural amplitude and frequency of the subject's breathing was extracted from the data set collected. In all of the training sessions, time-averaged data from the free breathing pattern were used in order to establish the parameters of a regular training pattern which called the synthetic breathing patterns or synthetic breathing patterns that will be used during the video biofeedback.

Video biofeedback breathing session

For video biofeedback breathing, the subject's chest expansion during free breathing was recorded and analyzed to determine the appropriate frequency of the video biofeedback to form synthetic breathing patterns. The subject was presented with synthetic pattern (synthetic) that has been created from the free breathing session. The subject was asked to follow his/her real breathing and to try to match it with the synthetic breathing. The real breathing was shown to the subject on a flat screen monitor which had been fitted to a medical stand and which the subject was able to adjust according to his/her position and vision, so that he or she could see the breathing trace very clearly; the idea behind this was that the subject should attempt to make his/her pattern follow as closely as possible the guiding (or synthetic) waveform, which took the form of a sine wave. Upper and lower guidelines were also placed on the rolling graph (just above and below the maximum inhalation and minimum exhalation phases of the synthetic waveform) in such a way as to act as an envelope within which the subjects were asked to keep their breathing amplitude. They were asked to try to follow the synthetic sinusoid for four minutes.

Statistical analysis

All the timestamps and sensor readings for each of the twelve subjects and the two breathing maneuvers (that is, free breathing without mentoring and breathing with video biofeedback mentoring)

Figure 1. The breathing device that was built for this study.

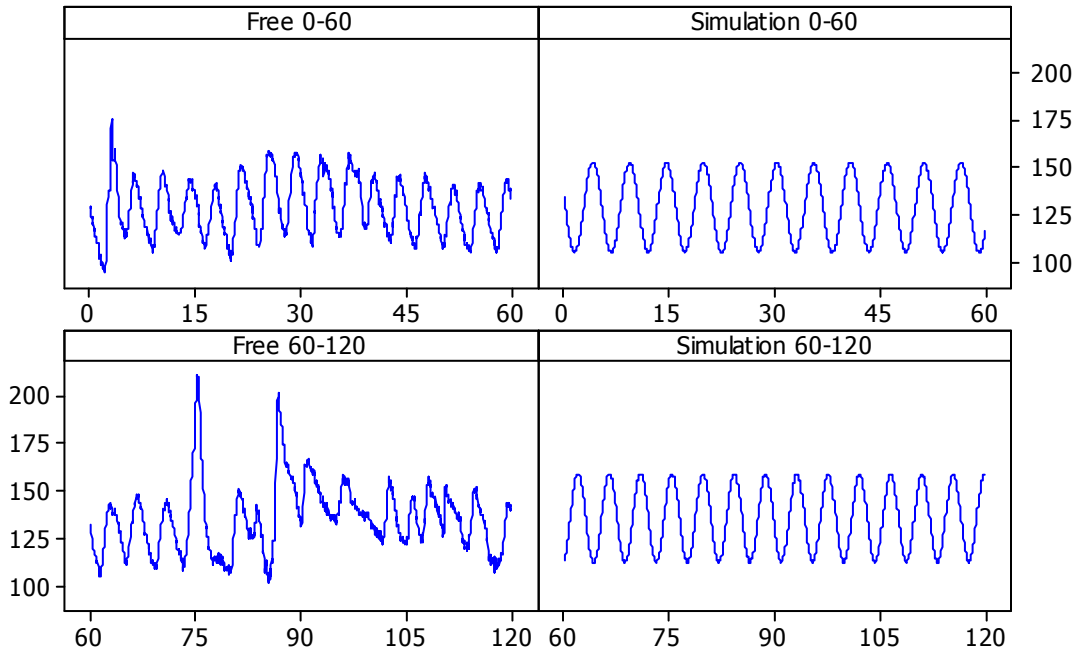

Figure 2. Comparison of real and simulated data (Subject D2; 0-60; 60-120 s).

were collated into one spreadsheet. All readings collected after 240 s were excluded from statistical analysis. Time-series plots to display each set of sensor readings for 240 s were collated, so that subjective visual comparisons of the variations in breathing patterns could be performed. The first 240 s of each set of sensor readings were split into four equal sections that is, as shown in Figure 2. The duration of each section was 60 s. This provided four replicates or repeated measures of the breathing patterns (that is, variations in breathing parameters with respect to time) with exactly the same sample size in each equal time section. The extraction of four

samples of equal size from each data set ensured that, for purposes of statistical comparison, the experimental design was balanced. Balanced designs help to increase the power of statistical tests. Each 60-s section of data was plotted as a time series, and analyzed separately. A sine wave model was fitted to each data set, using the following formula:

$$Yt = C + \alpha \sin(\omega t + \varphi)$$

Where Yt is simulated sensor reading at time (t); C is baseline constant (approximated initially by the average sensor reading over the 60-s time period); α is an amplitude (approximated initially by the deviation above and below the baseline caused by inhalation and exhalation), ω is the angular frequency, corresponding to the average number of inhalations and exhalation cycles (in radians) in the 60 s time period, t is a function of the timestamp, φ is the average angular phase-shift (in radians) corresponding to the change in time period between successive cycles of inhalation and exhalation.

To extract the model parameters from each set of data, a spectral analysis of the breathing patterns was performed using GraphPad® Prism (Graphpad Software, Sorrento Valley, San Diego, CA, USA). The final solution to each sine wave model was the optimum line of fit, derived from the smallest sums of squares between the observed sensor readings and the data simulated by the model. The best line of fit was converged upon by iteration (that is, after initialization with average values, the computer then tried out many different parameter values, until an optimum solution was reached). The goodness of fit was indicated by comparing the observed breathing data with the data simulated by the sine wave model. The R2 statistic, expressed as a percentage, (corresponding to the proportion of the variation in the real data which was explained by the model) was used for this purpose. The closer the R2 value was to 100%, then the closer the fit the model was to the real data. Further statistical analysis was performed using Minitab ® (Minitab Inc., Enterprise Drive, State College, PA USA).

The aim was to test the hypothesis that there were no significant effects of the three factors that is, (1) twelve random subjects (2) four different times (the repeated measures) and (3) two different types of breathing (free and video) on the four computed breathing parameters (C, α, ω, and φ). Multi-factorial repeated measures ANOVA (assuming a General Linear Model with a balanced design) was used to determine the effects of the three factors on the four response variables. Post-hoc analyses were performed using Tukey's method for the pair-wise comparison of mean values. ANOVA with repeated measures was applicable because the data violated the assumption of independence (Independence means that the data in one replicate sample do not have any influence upon the data in another replicate sample). The breathing observations were not independent because they were repeated over time (that is, four replicate 60-s sensor reading samples were obtained within a total time period of 240 s for each of the twelve subjects, and for each of two breathing control methods). Consequently, during the 240-s time period used for each set, the values of the breathing parameters in previous samples may have influenced the corresponding values in subsequent samples. The random effects of the subjects (the inherent variability of the breathing parameters within and between subjects over a period of time) which might otherwise influence the results of the ANOVA were also taken into account.

RESULTS

Table 1 shows parameters computed to fit the sine wave model to free breathing sensor readings for 12 subjects without video mentoring. Table 2 shows parameters computed to fit the sine wave model to breathing sensor readings for 12 subjects with video mentoring. Figure 3 shows visual comparison of the breathing patterns of the 12 subjects (sensor readings plotted on time in seconds) for the two treatments: free breathing (without mentoring) and video biofeedback. The results showed that the first stage of the analysis was to make a simple subjective overview of the breathing sensor readings for each of the twelve subjects and the two breathing modalities with respect to time.

It can be concluded from subjective visual observation of Figures 6 and 7 that video mentoring appeared to change and generally stabilize the breathing patterns in most of the subjects, when compared with the high diversity of free breathing patterns observed in subjects without mentoring. This simple overview provides justification for performing statistical tests to determine objectively whether the apparent differences in breathing patterns observed in Figure 3 are really significant.

DISCUSSION

The literature attests to the fact that techniques such as deep inspiration breath hold (DIBH), deep expiration breath holds (DEBH) and chest restrictors are not well tolerated by lung cancer patients (Kini et al., 2003; Rosenzweig et al., 2000; Kima et al., 2007), who often have some form of lung dysfunction (Neicu et al., 2006). This obvious difficulty has led to the development of techniques which have attempted to capitalize on the patient's free breathing. However, it seems that the search for a technological solution has, to some extent, outstripped the evidence as to the best way to train a patient to breathe in a regular and controlled fashion, thus missing the potential for a simple solution to the problem of monitoring chest wall motion. While this clearly ignores the potential weakness of the assumption that tumor motion and chest wall motion are indeed correlated, this is nevertheless considered to be beyond the scope of the current study.

The goals of the study were to develop a non-invasive device that could mentor the subject breathing during the radiation therapy treatment. This device has to be a free stand device, which means it has to be fully functioning without any other accessories or machines. Then the second goal was to establish breathing patterns that will help the patients during the lung cancer treatment with radiation therapy to control their breaths without the need for extra accessories or extra complicated techniques, which then would let to improve the outcome of the treatments. The developing of the device went under investigations before coming to the final that used with volunteered subjects to monitor the breathing patterns. These investigations involve the choosing of the suitable

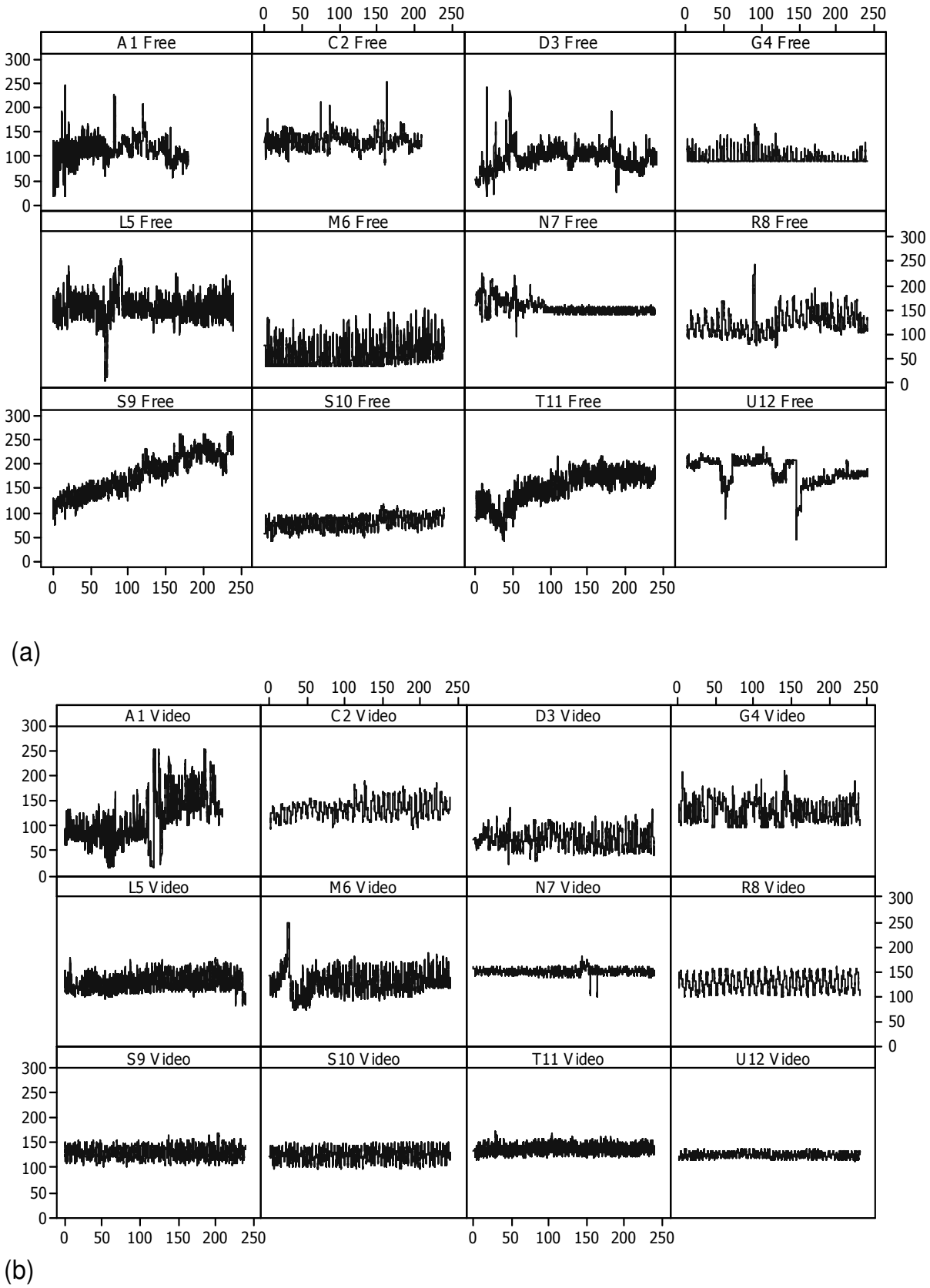

Figure 3. Visual comparisons of the breathing patterns of the 12 subjects (sensor readings plotted on time in seconds) for the two treatments (a) free breathing (without mentoring) and (b) video feedback.

Table 1. Parameters computed to fit the sine wave model to free breathing sensor readings for 12 subjects without video mentoring.

Subject	Time (s)	C	α	ω	φ	R2 (%)
A1	0-60	107.6	25.7	0.96	3.11	45.6
	60-120	119.9	20.1	1.04	-4.56	28.4
	120-180	107.5	23.4	1.16	-24.4	26.2
C2	0-60	128.8	21.9	1.12	-3.36	73.9
	60-120	135.8	27.1	0.96	4.39	53.2
	120-180	127.8	25.8	0.98	-10.22	16.4
	180-240	129.3	15.9	0.92	16.1	62.0
D3	0-60	79.1	29.1	0.60	1.75	29.5
	60-120	102.5	23.8	1.06	-4.24	70.9
	120-180	102.5	15.6	0.99	0.20	67.5
	180-240	91.4	26.7	1.08	0.46	38.4
G4	0-60	96.7	16.1	1.48	-4.57	64.7
	60-120	97.5	17.3	0.74	17.23	73.2
	120-180	95.6	12.9	1.33	-4.39	88.3
	180-240	97.9	18.2	0.97	1.66	71.4
L5	0-60	154.2	16.4	0.70	2.17	97.3
	60-120	156.3	15.4	1.22	-12.98	76.3
	120-180	152.6	17.9	1.06	-9.31	97.7
	180-240	153.3	15.7	0.93	13.46	84.7
M6	0-60	53.1	17.7	1.4	1.64	61.5
	60-120	54.8	19.2	1.1	-10.2	72.1
	120-180	62.4	25.8	1.4	-5.58	76.9
	180-240	72.9	24.6	1.3	10.3	69.6
N7	0-60	169.9	20.8	0.79	-0.32	35.5
	60-120	156.1	22.1	1.09	28.29	28.3
	120-180	149.2	14.1	1.62	-9.15	56.9
	180-240	151.3	14.6	1.30	26.86	93.7
R8	0-60	116.8	30.0	0.72	2.94	74.8
	60-120	109.3	13.3	1.26	-21.4	67.6
	120-180	138.2	22.4	0.91	12.94	61.9
	180-240	133.3	25.8	1.00	1.51	78.4
S9	0-60	119.5	24.5	0.83	-16.57	54.7
	60-120	150.1	15.9	1.15	-11.39	78.5
	120-180	201.1	28.1	1.45	7.13	74.9
	180-240	223.7	24.6	1.30	-0.49	81.6
S10	0-60	71.5	11.7	1.53	-6.49	28.5
	60-120	80.2	13.1	1.70	-28.20	82.3
	120-180	80.5	15.9	1.48	22.91	85.5

The complete set of sensor readings was not available for 180-240 s for subject A1.

Table 2. Parameters computed to fit the sine wave model to breathing sensor readings for 12 subjects with video biofeedback mentoring.

Subject	Time (s)	C	α	ω	φ	R2 (%)
A1	0-60	83.3	26.1	1.08	-3.71	74.8
	60-120	85.7	63.6	0.98	4.37	52.6
	120-180	150.0	45.8	0.93	9.59	54.1
C2	0-60	128.2	21.3	1.02	-2.79	76.4
	60-120	132.6	21.4	1.07	-8.46	79.8
	120-180	137.0	26.9	0.87	2.31	59.8
	180-240	137.0	27.5	0.90	5.00	58.2
D3	0-60	73.5	24.5	0.80	8.07	68.1
	60-120	73.9	28.4	0.89	6.99	69.1
	120-180	68.3	37.8	1.07	-11.04	92.5
	180-240	71.4	35.6	1.01	0.07	99.1
G4	0-60	136.9	23.9	1.06	2.05	41.1
	60-120	124.9	24.1	0.90	26.11	48.4
	120-180	126.0	18.5	1.14	21.05	67.5
	180.240	127.3	25.8	1.19	26.08	59.9
L5	0-60	122.7	30.5	0.70	1.95	77.7
	60-120	127.6	19.6	1.15	-13.26	84.8
	120-180	133.9	21.2	0.95	13.13	85.2
	180-240	131.8	27.3	1.06	0.85	85.9
M6	0-60	127.4	23.3	0.81	3.42	72.1
	60-120	131.6	30.5	1.01	-7.13	69.8
	120-180	129.1	30.4	1.28	-37.18	80.5
	180-240	137.0	26.5	0.93	14.26	92.3
N7	0-60	151.1	5.1	1.12	-3.86	55.9
	60-120	150.1	7.2	1.05	-1.97	80.1
	120-180	150.9	20.2	0.78	34.26	75.2
	180-240	151.1	7.1	1.04	-6.71	99.4
R8	0-60	127.9	19.9	0.71	2.59	89.7
	60-120	129.8	22.4	0.77	14.8	96.8
	120-180	128.2	25.5	0.89	16.73	82.5
	180-240	128.9	23.9	1.07	-12.53	92.8
S9	0-60	130.2	22.2	1.12	-0.43	89.5
	60-120	132.4	16.2	1.10	16.66	86.7
	120-180	133.6	17.3	1.20	25.7	90.5
	180-240	132.3	17.7	1.12	-10.82	75.1
S10	0-60	124.9	15.9	1.10	-1.02	80.9
	60-120	124.5	17.9	1.24	-24.24	92.8
	120-180	127.9	21.7	0.99	1.14	90.7
	180-240	128.1	18.4	0.75	56.61	88.9
T11	0-60	135.0	17.0	1.10	-21.87	81.5
	60-120	140.5	15.2	1.11	-8.83	73.5
	120-180	140.0	11.9	0.88	14.98	85.0
	180-240	139.4	10.6	1.07	-15.71	91.2
U12	0-60	126.8	7.89	1.14	-2.52	80.8
	60-120	127.7	5.60	1.13	-21.40	80.6

Table 2. Contd.

120-180	127.1	9.2	1.03	-2.56	89.4
180-240	148.1	13.7	1.20	4.29	50.8

The complete set of sensor readings was not available for 180-240 s for subject A1.

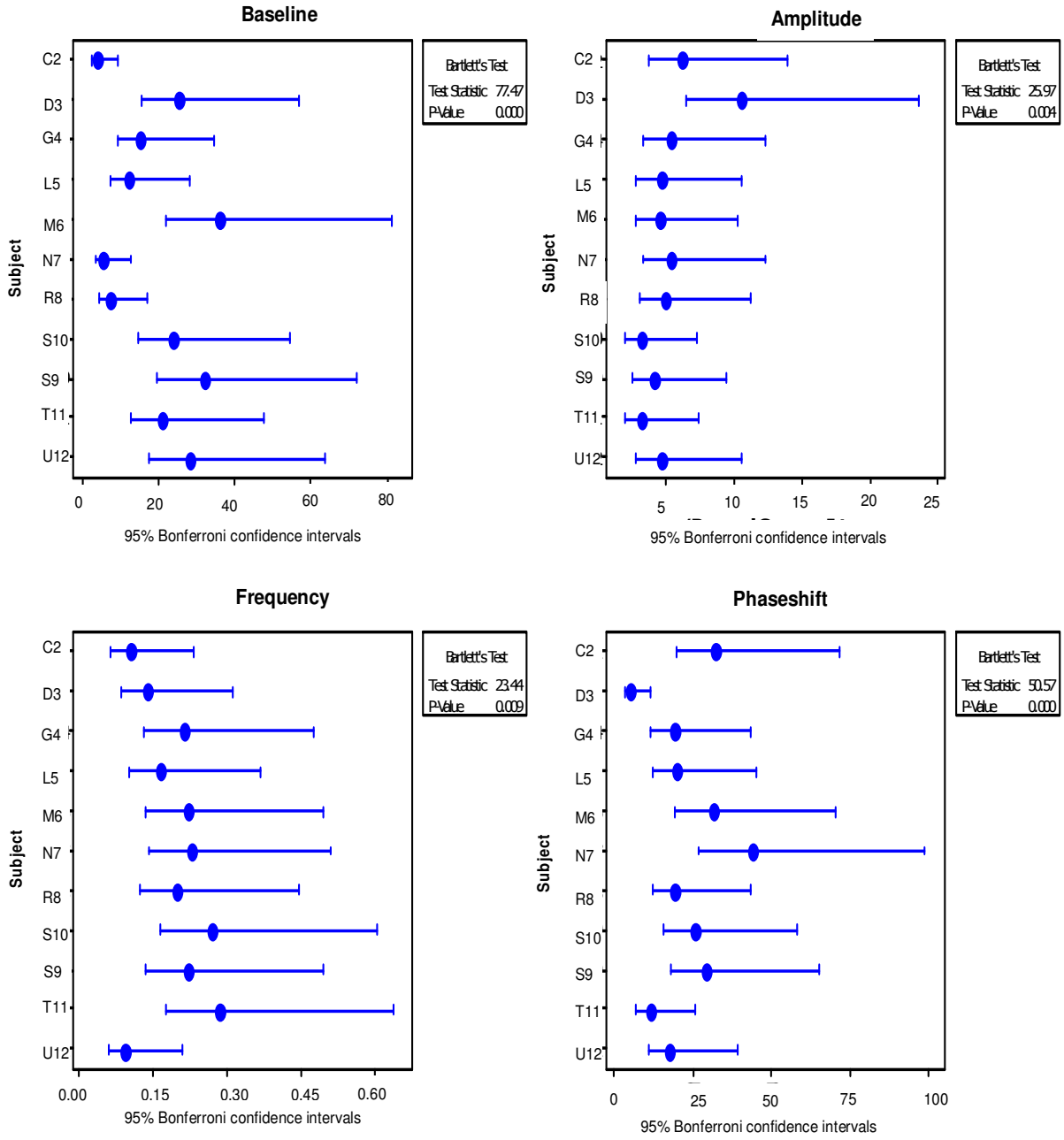

Figure 4. Variance in C, α, ω, and φ with respect to subjects.

sensor that could use with the device to detect the chest movement. The investigation and testing included the device material, parts, and finally the software that enable it to record and analyze the breathing data of participants. The first stage of the analysis was to make a simple subjective overview of the breathing sensor readings for each of the twelve subjects and the two breathing maneuvers (free and video biofeedback breathing) with respect to time. The device we used was a custom made belt and a variable resistive element constructed from a rubber capillary tube and a liquid metal filling, and an operational amplifier. A strain gauge sensor was placed

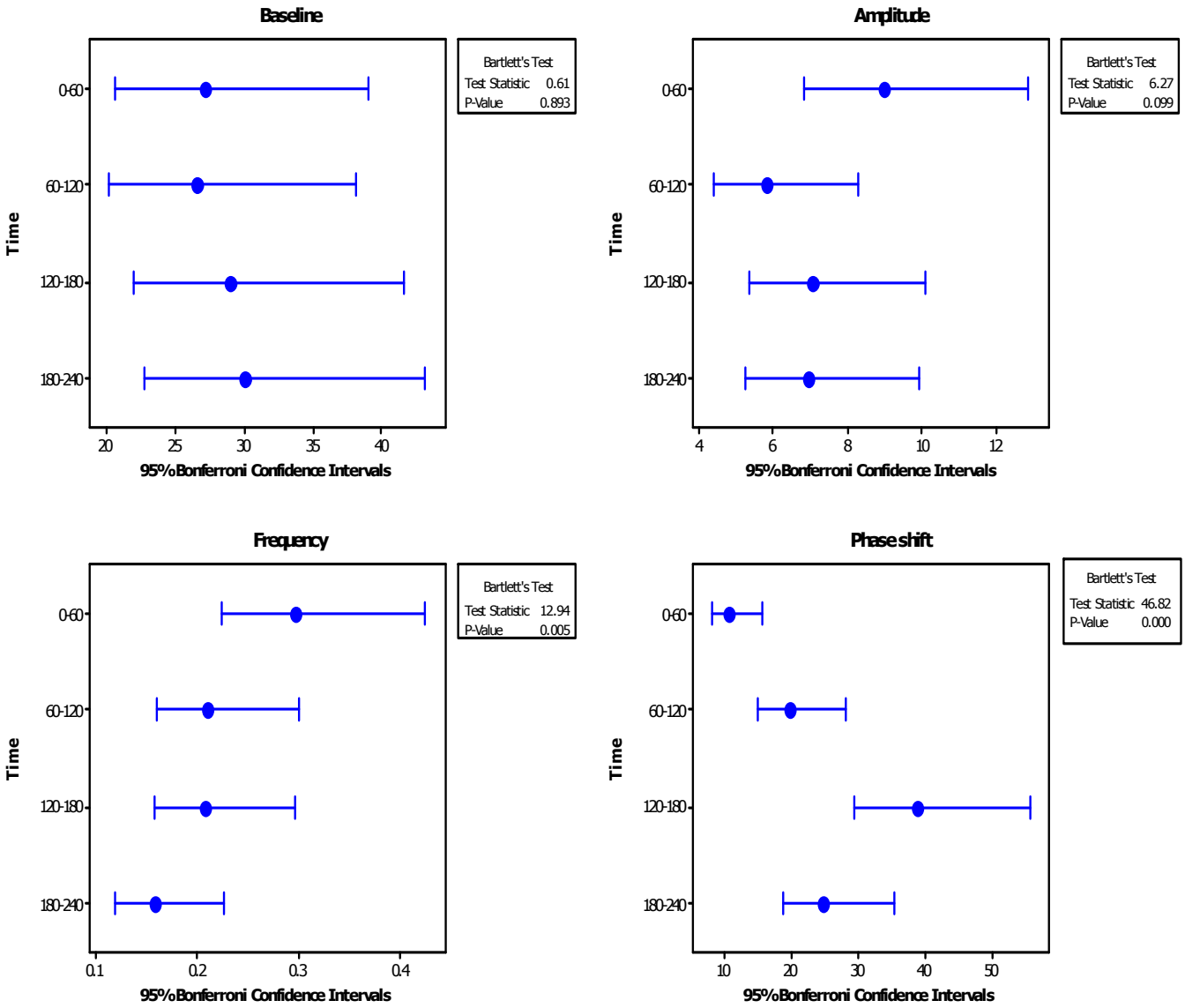

Figure 5. Variance in C, α, ω, and φ with respect to time.

on a belt and use simple electronics in order to monitor chest expansion. The output of the sensor was directly fed into a simple amplification circuit using an operational amplifier prior to analogue-to-digital conversion (ADC); then fed to a personal computer (PC) to control the whole system with the use of a custom-built software package. The device is friendly to use, easy-to-operate, and a cost-effective device. The study was conducted in twelve health volunteer subjects.

To maintain anonymity, and provide concise labels in Tables and Figures, the 12 subjects were coded with names A1, C2, D3, G4, L5, M6, N7, R8, S9, S10, T11, and U12 as shown in Tables 1 and 2 for the two breathing control methods (free breathing and video biofeedback). The first 240 s of sensor readings collected from each subject and each breathing maneuver were extracted. It can be concluded from the subjective visual observation of Figure 2 video mentoring appeared to change and generally stabilize the breathing patterns in most of the subjects, when compared with the high diversity of free breathing patterns observed in subjects without mentoring. Our results are similar to those obtained by Kini et al. (2003), Keall (2006) and Neicu et al. (2006) who found that patient coaching, using audio prompting or video biofeedback, would improve the breathing patterns and ultimately increase the reproducibility. The result of the study showed that the breathing patterns varied between the subjects and between every breathing coaching modality which are the free breathing and video biofeedback. However, video

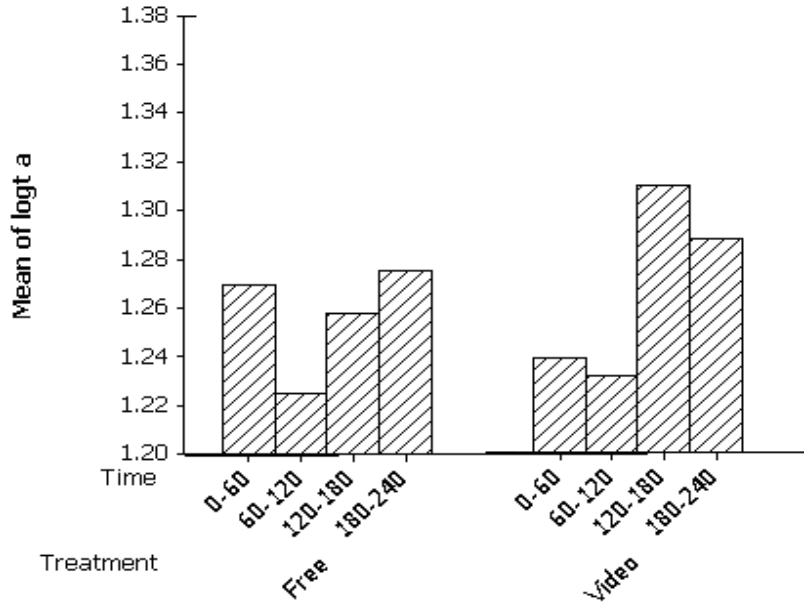

Figure 6. Comparison of mean amplitudes with respect to time and treatment.

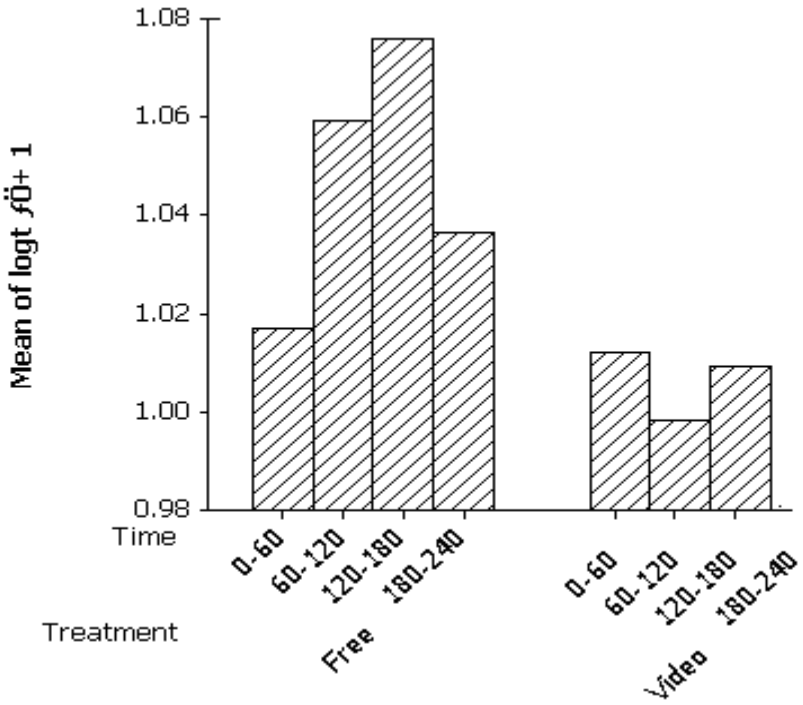

Figure 7. Comparison of mean frequencies with respect to time and treatment.

biofeedback showed more stable breathing patterns. The amplitude for coached breathing with video biofeedback is slightly better than that for the free breathing.

Comparison of the variances of the sine wave model parameters C, α, ω, and φ

The variability in the sine wave model parameters with respect to subjects, times, and breathing methods control as shown in Figure 3 was determined by their variances ± 95% Bonferroni confidence intervals. The results of Bartlett's test for equality of variance were recorded to determine if the variances were significantly different between subjects, times, and treatments. The data for subject A1 were excluded from this analysis, since a complete set of sensor readings was not available for this

subject, thereby creating an unbalanced design. There was significant variability within and between the subjects in the baselines, amplitudes, frequencies, and phase shifts. The P values for Bartlett's test for equality of variance were all < 0.01, indicating that highly significant differences between the variances with respect to the different subjects for all of the breathing parameters extracted from the sine wave models. This implies that a significant source of variance in the breathing patterns was the inherent differences within and between the subjects, and these results must be taken into account when performing ANOVA.

Computation of model parameters

The computed breathing parameters C, α, ω, and φ were tabulated for each of the twelve subjects, and for each of the two treatments, at the four specified time intervals (Tables 1 and 2). The variable R2 statistics indicated that the goodness of fit of the models varied widely. Nevertheless, significant breathing parameters were extracted for all of the samples.

The baselines, amplitudes, frequencies, and phase shifts also varied within and between the four replicate time periods of observation (Figures 4 and 5). The P values for Bartlett's test was on the baselines were ≥ 0.01, indicating that no significant differences between the variances of the baselines with respect to time. However, the P values were < 0.01 for the equality of variance test on the amplitudes, frequencies and phase shifts, indicating highly significant differences between the variances of these breathing parameters with respect to time. The variability in amplitude and frequency was generally highest during the first time period (0-60 s) then subsequently declined with respect to time. In contrast, the variance in phase shift tended to increase with respect to time. The results of Bartlett's tests implied that the significant differences between the variances in the breathing parameters with respect to time must be taken into account when performing ANOVA.

Conclusion

A low-cost device has been developed that could be used to monitor the patients during the radiation therapy treatment to control and stabilizing the breathing patterns. The device has a rapid response and produces accurate and reproducible signals during the breathing. In the same time the two methods of breathing maneuvers have been compared to evaluate the best way to stabilized the breathing which in other hand, would decrease the intra-fraction and increase the reproducibility and regularity of their breathing pattern. The two breathing maneuvers were the free breathing and video biofeedback breathing. It can be concluded from the subjective visual observation that video biofeedback breathing appeared to change and generally stabilize the breathing patterns in most of the subjects. Further work needed to be done to implement the device in clinic use and to use it with actual non small cell lung cancer to see the effective of breathing maneuver in chest movement during the treatment.

ACKNOWLEDGMENTS

The author would like to thank our participants and also the author would like to thank the Ministry of Higher Education, Riyadh, Saudi Arabia and King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia for supporting this study.

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