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Physiologically guided approach to characterizing respiratory motion

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Purpose: To characterize radiation therapy patient breathing patterns based on measured external surrogate information.
Methods: Breathing surrogate data were collected during 4DCT from a cohort of 50 patients including 28 patients with lung cancer and 22 patients without lung cancer. A spirometer and an abdominal pneumatic bellows were used as the surrogates. The relationship between these measurements was assumed to be linear within a small phase difference. The signals were correlated and drift corrected using a previously published method to convert the signal into tidal volume. The airflow was calculated with a first order time derivative of the tidal volume using a window centered on the point of interest and with a window length equal to the CT gantry rotation period. The airflow was compared against the tidal volume to create ellipsoidal patterns that were binned into 25 ml × 25 ml/s bins to determine the relative amount of time spent in each bin. To calculate the variability of the maximum inhalation tidal volume within a free-breathing scan timeframe, a metric based on percentile volume ratios was defined. The free breathing variability metric (κ) was defined as the ratio between extreme inhalation tidal volumes (defined as >93 tidal volume percentile of the measured tidal volume) and normal inhalation tidal volume (defined as >80 tidal volume percentile of the measured tidal volume).
Results: There were three observed types of volume-flow curves, labeled Types 1, 2, and 3. Type 1 patients spent a greater duration of time during exhalation with $\kappa = 1.37 \pm 0.11$. Type 2 patients had equal time duration spent during inhalation and exhalation with $\kappa = 1.28 \pm 0.09$. The differences between the mean peak exhalation to peak inhalation tidal volume, breathing period, and the 85th tidal volume percentile for Type 1 and Type 2 patients were statistically significant at the 2% significance level. The difference between κ and the 98th tidal volume percentile for Type 1 and Type 2 patients was found to be statistically significant at the 1% significance level. Three patients did not display a breathing stability curve that could be classified as Type 1 or Type 2 due to chaotic breathing patterns. These patients were classified as Type 3 patients.
Conclusions: Based on an observed volume-flow curve pattern, the cohort of 50 patients was divided into three categories called Type 1, Type 2, and Type 3. There were statistically significant differences in breathing characteristics between Type 1 and Type 2 patients. The use of volume-flow curves to classify patients has been demonstrated as a physiological characterization metric that has the potential to optimize gating windows in radiation therapy. © *2013 American Association of Physicists in Medicine*. [http://dx.doi.org/10.1118/1.4830423]

Key words: tidal volume, airflow, respiratory gating

1. INTRODUCTION

Human breathing patterns have been a topic of interest for a long time.[1–17] Initial studies were conducted by Golla and Antonovitch in 1929.[1] They found that individuals had breathing patterns that were consistently regular or irregular.[1] The possibility of classifying human respiratory motion was demonstrated. The first concept of stable individuality in breathing patterns was introduced by Dejours *et al.*[2] in 1961. Improvements in technology facilitated more quantitative studies of breathing patterns.[3–17] Tobin *et al.*[15,16] conducted the first quantitative study of breathing patterns for healthy and diseased subjects using a spirometer mouth piece to measure the tidal volume. They noted a clear difference in breathing pattern between healthy and diseased subjects.[15,16] They investigated the breathing characteristics of the patient cohort that included 65 healthy individuals (18 individuals over 60 years old), 22 asymptomatic smokers, 17 asymptomatic asthmatic patients, 15 symptomatic asthmatic patients, 28 chronic obstructive pulmonary disease patients, and 14 restrictive lung disease patients. The study found no significant difference in breathing period, tidal volume, and airflow among the healthy subjects subdivided by the subject's sex or age. Smokers had increased tidal volume and decreased airflow compared to normal subjects. Asymptomatic asthmatic patients had no difference in the breathing characteristics compared to normal subjects. Symptomatic asthmatic patients had greatly increased tidal volume and airflow but a normal breathing period. Patients suffering from chronic obstructive pulmonary disease had increased breathing period, tidal volume, and airflow. Finally, they found patients with restrictive pulmonary disease had increased breathing period and airflow while also having a normal tidal volume compared to healthy subjects. These studies were not conducted for a radiotherapy patient cohort. A long term study conducted by Benchetrit *et al.*[5] demonstrated that the breathing patterns of healthy subjects were reproducible for the same individual despite 4–5 years between study sessions. This led Benchetrit *et al.*[5] to conclude that despite an infinite combination of breathing variables, each individual had a single stable pattern that was consistent over a long period of time.[4] While breathing patterns exhibited a high degree of diversity, there was a resemblance between individuals[4] which could allow classifications into groups with similar characteristics.

This work investigated quiet respiration breathing patterns measured using two synchronized external surrogates to evaluate if the breathing patterns could be broadly characterized for radiotherapy patients. Characterization of breathing patterns and the observed breathing variability during a single treatment session should be useful for optimizing respiratory gating methods.

2. METHODS

2.A. Data collection

Breathing data were collected from 50 radiotherapy patients, 28 lung cancer patients, and 22 nonlung cancer patients while they were undergoing research 4DCT procedures.[17–22] Patients were enrolled in this protocol under the criteria that each had biopsy-proven or suspected cancer and was prescribed at least 45 Gy photon-based radiation therapy to the gross tumor volume. Breathing tidal volume was measured using two simultaneously acquired breathing surrogates, a spirometer and a pneumatic bellows, gathered for more than 300 s. The spirometer was a commercial device (VMM400, Interface Associates) and consisted of a mouthpiece, tubing, and a small turbine connected to the system electronics. The spirometer electronics provided an analog voltage signal proportional to airflow that was read by an ADC board (BNC 2110, National Instruments) with a 0.01 s sampling interval. Under constant airflow conditions, the system accuracy was within 3% as reported by Lu *et al.*[23] For breathing measurements, the spirometer had substantial drift artifacts that required the use of an additional breathing metric. To account for the spirometer signal drift, an air-tight cylindrical bellows shaped tube (76513NM10, Lafayette Instrument Co.) was wrapped around the abdomen; air pressure variation inside the bellows during respiration was measured by a built-in pressure transducer providing a voltage signal proportional to the air pressure. The same analog-to-digital converter that monitored the spirometer monitored the bellows voltage signal.[20] The quality of this data collection process has been discussed in detail in previous publications.[17,19,20,22]

2.B. Data processing

The spirometer-measured tidal volume exhibited a baseline drift and had a signal that if analyzed from sample to sample without additional processing would yield derivative measurements whose noise level would exceed the natural rate variation.[20] To remove the spirometer baseline drift, a piecewise linear regression between the spirometer and bellows signals was independently calculated over 18.2 s sliding windows (the length of the sliding window was approximately equal to the 4DCT scanning duration at each couch position). The bellows signal drift correction and a small time offset (to model the time delay between abdominal motion and airflow) were determined by maximizing the correlation coefficient between the two signals for each 18.2 s time window. Werner *et al.*[20] had used the same patient dataset for 4DCT analysis and determined that both signals were linearly related to the CT-based air content.

The tidal volume was smoothed using a fifth order polynomial over a time period corresponding to a single CT gantry rotation (0.46 s) and centered on the point where the airflow was being determined. A fifth order polynomial was selected because it provided the lowest order polynomial that maintained a good fit to the airflow result. The airflow was the time derivative of the smoothed tidal volume signal.

2.C. Breathing data evaluation

The goal of this study was to characterize respiration into categories that could be useful for treatment and treatment planning. Breathing variations were examined by plotting the airflow against the tidal volume to create volume-flow curves, representing individual breaths as elliptically shaped loops. The breathing cycle probability density distribution for an entire data collection session was created from the volume-flow curves and segmented into 25 ml and 25 ml/s volume and flow bins, respectively. The bin size was chosen to provide at most approximately 1% in each bin of the data points from the entire scanning session. These volume-flow curves were compared between patients to determine if any patterns emerged. The breathing traces of lung cancer and nonlung cancer patients were compared to determine if there were statistically significant differences between the two populations. The evaluated metrics were breathing period, peak-to-peak tidal volume, average maximum exhalation tidal volume, average maximum inhalation tidal volume, average extreme inhalation tidal volume, and the ratio of time spent inhaling to the time spent exhaling. Maximum exhalation and inhalation tidal volumes were defined at the fifth (v_{05}) and 85th tidal volume percentiles (v_{85}), respectively. The statistical significance of the differences between the listed metrics for the patients was assessed with a two-tailed Student T test. Using tidal volume percentiles provided a consistent method of defining tidal volume extremes and the selected values encompassed 80% of the respiratory signal. The extreme inhalation tidal volumes were defined as volumes extending beyond the 98th tidal volume percentile, v_{98}. To investigate the variability within a free breathing scan timeframe, a metric based on percentile volume ratios was defined. The free breathing variability metric (κ) was defined as the ratio

$$k = \frac{v_{98} - v_5}{v_{85} - v_5}. \tag{1}$$

κ was developed to gauge the difference between extreme tidal volume inhalations ($v_{98} - v_5$) and normal tidal volume inhalations ($v_{85} - v_5$). A two-tailed Z test was performed to check the statistical difference between Type 1 and Type 2 patients.

3. RESULTS

The breathing probability distributions showed that they could be characterized by whether the patient spent less than, equal, or more time during inhalation than exhalation. Out of 50 patients, the volume-flow curves showed that none of the patients spent more time during inhalation than exhalation, 34 of the patients spent more time during exhalation (termed Type 1), and 13 patients spent roughly the same time during inhalation as exhalation (termed Type 2). Volume-flow probability distributions for both observed types of respiratory patterns are shown in Fig. 1. The average values of κ for Type 1 and Type 2 patients were 1.37 ± 0.11 and 1.28 ± 0.09, respectively. The mean tidal volumes for Type 1 and Type 2 patients were 602 ± 275 and 409 ± 99 ml, respectively. The mean breathing periods were 4.9 ± 2.0 and 3.5 ± 0.6 s per breath, for Type 1 and Type 2 patients, respectively. The average ratio of time spent inhaling to time spent exhaling was 0.71 ± 0.13 and 0.97 ± 0.04 for Type 1 and Type 2 patients, respectively. A two-tailed Student Z test found the mean tidal volume, breathing period, v_{98}, and v_{85} to be statistically different at the 5% significance level ($p < 0.05$). The test did not find a statistically significant difference in the mean breathing amplitude, mean breathing period, and κ.

Among the 28 lung cancer patients, there were 21 Type 1 patients and six Type 2 patients. The average κ for those Type 1 and Type 2 patients were 1.39 ± 0.12 and 1.26 ± 0.07, respectively. The mean peak to peak amplitudes were 557 ± 257 and 442 ± 110 ml for Type 1 and Type 2 patients, respectively. The mean breathing periods for Type 1 and Type 2 patients were 4.5 ± 2.0 and 3.6 ± 0.6 s per breath, respectively. The lung cancer patients had an average κ of 1.36 ± 0.12, mean peak to peak amplitude of 520 ± 131 ml, and a mean breathing period of 4.30 ± 1.95 s per breath. The two tailed Student Z test found no statistically significant difference between Type 1 and Type 2 patients with lung cancer.

Among the 22 nonlung cancer patients, there were 12 Type 1 patients and eight Type 2 patients. The average κ for those Type 1 and Type 2 patients were 1.34 ± 0.08 and 1.30 ± 0.12, respectively. The mean peak to peak amplitudes were 676 ± 297 and 357 ± 54 ml for Type 1 and Type 2 patients, respectively. The mean breathing periods were 5.7 ± 1.9 and 3.3 ± 0.7 s per breath for Types 1 and 2 patients, respectively. The nonlung cancer patients had an average κ of 1.32 ± 0.09, mean peak to peak amplitude of 592 ± 268 ml, and a mean breathing period of 4.8 ± 1.8 s per breath. The two tailed Student Z test found no statistically significant difference between Type 1 and Type 2 patients without lung cancer. A summary of the results can be seen in Table I.

Out of the 50 patients, three displayed chaotic breathing tendencies. We termed these patients as Type 3 patients. Because of their wide respiration variability and a sample size of only three patients, no meaningful statistical analysis could be applied to the Type 3 patients.

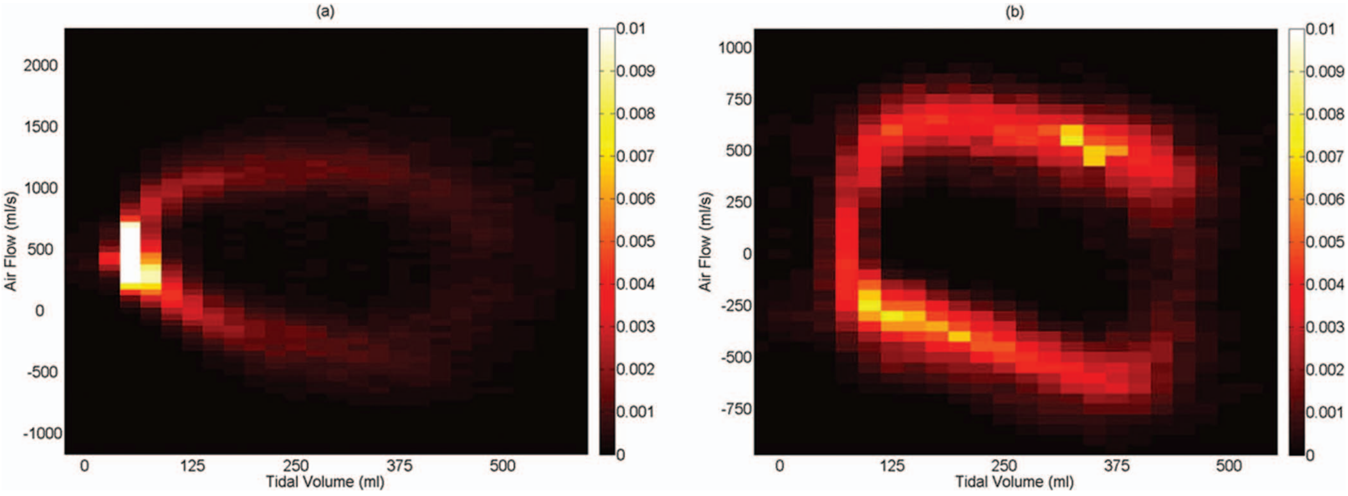

FIG. 1. Volume-flow curves for two patients in the study. An example of a Type 1 (a) patient and a Type 2 (b) patient is shown with the color-bar denoting the percentage of time the patient spent in a given 25 ml and 25 ml/s volume and flow bin.

TABLE I. Summary of the statistics for nonlung cancer and cancer patients separated into Type 1 and Type 2 subsets. Note: Type 3 patients are not displayed.

Type 1 patients	Number of patients	κ	Peak to peak amplitude (ml)	Breathing period (s)
All	34	1.37 ± 0.11	602 ± 275	4.9 ± 2.0
Lung cancer	21	1.39 ± 0.12	557 ± 257	4.5 ± 2.0
NLC	13	1.34 ± 0.08	676 ± 297	5.7 ± 1.9
Type 2 patients	Number of patients	κ	Peak to peak amplitude (ml)	Breathing period (s)
All	13	1.28 ± 0.09	409 ± 99	3.5 ± 0.6
Lung cancer	8	1.26 ± 0.07	442 ± 110	3.6 ± 0.6
NLC	5	1.30 ± 0.12	357 ± 54	3.3 ± 0.7
Combined patients	Number of patients	κ	Peak to peak amplitude (ml)	Breathing period (s)
All	50	1.34 ± 0.11	552 ± 257	4.5 ± 1.9
Lung cancer	28	1.36 ± 0.12	520 ± 131	4.3 ± 2.0
NLC	22	1.32 ± 0.09	592 ± 268	4.8 ± 1.8

4. DISCUSSION

The difference between Type 1 and Type 2 patients was statistically significant at the 2% significance level for the mean peak exhalation to peak inhalation tidal volume ($p = 0.018$), breathing period ($p = 0.014$), and v_{85} ($p = 0.014$). The difference between Type 1 and Type 2 patients was statistically significant at the 1% significance level for v_{98} ($p = 0.004$) and κ ($p = 0.007$). Observation of the volume-flow probability density provided an excellent metric to characterize individuals. Figure 1 displays the difference between Type 1 and Type 2 in terms of how long the patient spends in a given respiratory phase. Figure 1 shows the volume-flow curve for two patients in this study. Figure 1(a) shows a Type 1 breathing pattern and Fig. 1(b) shows a Type 2 breathing pattern.

Type 1 patients constituted 68% of the patients in this study. Type 1 individuals breathed in a pattern that was consistent with quiet respiration; in other words, respiration was not forced. In this group, only 18% of the patients had Stage III or higher lung cancer. This was in contrast with Type 2 patients in which 88% of the lung cancer cases had Stage III or greater lung cancer. Type 2 patients displayed mild dyspnea with exertions that decreased the breathing period and maximum exhalation to maximum inhalation tidal volume. These exertions caused the saw-tooth breathing pattern observed with Type 2 patients. This pattern is not normal for humans.[4,5] It is a taxing pattern that requires active exertions during both inhalation and exhalation.[4,5] The impact of using a spirometer as a respiratory surrogate has been discounted as the cause of the Type 2 pattern. Askanazi *et al.*[3] reported on the effect a mouthpiece and nose piece has on respiratory measurements. They reported a 15.5% increase in tidal volume and a 14.1% increase in airflow. They concluded that the respiratory load could be impacted by either the use of the spirometer and nose piece or sensory stimuli between the face, mouth, and nose contributed to the increased values. Since the respiratory data acquired for this study were consistent, the difference between Type 1 and Type 2 patients did not arise from the surrogate but from the respiratory pattern of the individual. The Type 3 patients constituted only 6% of the patients in this study. These patients displayed no discernible respiratory stability. The breathing traces were highly variable so the respiratory pattern was blurred with no single breathing phase displaying more stability. Published data have suggested patients with anxiety breathe with sporadic exertions at random respiratory phases, consistent with Type 3 patient breathing patterns.[3–5,24]

These results have important ramifications for phase-based breathing models. Phase based respiratory modeling assumes reproducibility in the breathing pattern. In addition to characterizing patients by breathing pattern type, κ provided a metric to quantify the difference between extreme tidal volume inhalations and normal tidal volume inhalations. Due to the respiratory exertions driving the breathing patterns of Type 2 patients, κ was smaller than Type 1 patients. This meant there was approximately 10% less variability in Type 2 patients at maximum inhalation than Type 1 patients. The reduced variability makes Type 2 patients potential end of inhalation and end of exhalation gating candidates for IMRT. This reduces the duration of the gated treatment session compared to Type 1 patients that appropriate gating candidates during end exhalation only. However, Type 1 patients spend the majority of the breathing cycle in a single phase which will make these patients optimal candidates for gating. Figure 2 displays the distribution of κ for Type 1 and Type 2 patients.

In the absence of coached breathing, classifying patients by breathing type has the potential to better define gating windows. For all patients in this study, gating at end of inhalation would increase the duration of the therapy session because of the short time the patients spent in this breathing phase. Gating at end of exhalation would be optimal for Type 1 patients (2/3 of patients) in our cohort. Use of an end exhalation gating window for the Type 2 patients (1/3 of patients) in our cohort would not provide an efficiency benefit over an end inhalation window. The potential to reduce the duration of gated radiotherapy treatments without coaching is valuable. Many patients with advanced stage lung cancer cannot

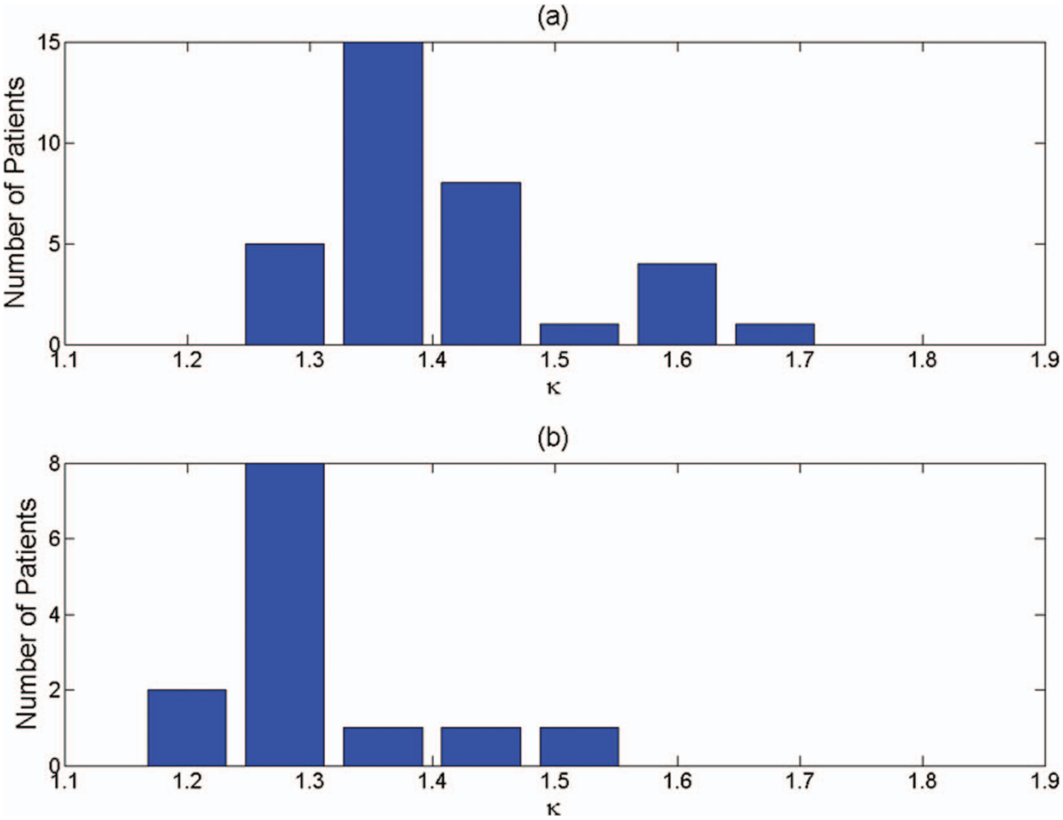

FIG. 2. Histograms displaying the free breathing variability metric (κ) for Type 1 (a) and Type 2 (b) patients.

maintain a reproducible breathing pattern despite coaching. A free breathing approach will ease the stress on the patient during the treatment session. This study provides a new metric that will aid in optimizing the efficiency of treatment gating windows used in clinical situations.

In this paper, the patient breathing pattern was characterized based on a physiologic quantity, tidal volume. The tidal volume was determined through the simultaneous use of a spirometer with an abdominal motion surrogate. Currently, most radiation oncology departments do not utilize a spirometer for 4DCT in the clinical setting. Techniques to find the tidal volume from a single abdominal distension surrogate have been previously investigated.[20,25] Both techniques demonstrated that the fundamental value of total volume to tidal volume expansion of the body provides a useful metric for a single abdominal surrogate approach. However, a qualitative analysis could be performed based on a single abdominal surrogate. Without tidal volume, a quantitative comparison between individuals is not possible. The advantage of using a physiologic quantity, tidal volume, can be seen in Fig. 1. It would not be possible to make a comparison between the curves in Fig. 1 based entirely on bellows voltage since that value will be relative to individual scanning sessions. With the relative bellows voltage, it will still be possible to obtain voltage percentiles for calculating the relative κ for each scanning session. This will provide useful information on the variability of respiration during the scanning session without the need to determine tidal volume.

5. CONCLUSION

A cohort of 50 radiation therapy patients with and without lung cancer was analyzed to characterize the patients using breathing surrogate measurement. Based on observed breathing stability curve patterns, the cohort was divided into three categories called Type 1, Type 2, and Type 3. Type 1 patients exhibited a volume-flow probability density peak at exhalation. Type 2 patients had roughly equal probability density during both inhalation and exhalation. Type 3 patients exhibited highly variable and chaotic breathing patterns, but comprised only 6% of the cohort. The free breathing variability metric (κ) showed the ratio of extreme inhalation tidal volume and normal inhalation tidal volumes to be 1.37 ± 0.11 and 1.28 ± 0.09 for Types 1 and 2, respectively. The classification of patient breathing type was shown to be novel and reliable characterization metric for optimizing the efficiency of gating windows during radiation therapy.

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