

Pulmonary-Impedance Power Spectral Analysis: A Facile Means of Detecting Radiation-Induced Gastrointestinal Distress and Performance Decrement in Man¹

Robert C. Ricks, C. C. Lushbaugh, Earl McDow

Oak Ridge Associated Universities

and

Edward Frome

Emory University

INTRODUCTION

It is common practice in routine physiologic monitoring of patients in intensive care units to measure respiratory rate and amplitude along with other vital signs by electronic means. In most respiratory studies the data are obtained through the use of impedance pneumography. This technique of measuring respiratory phenomena by means of electrical impedance has been previously described (refs. 1 and 2). These devices and techniques provide continuous analog and digital records of the patient's functional status and constantly updated visual displays of the data. Most often the values for the various vital sign measurements are displayed numerically on a cathode ray tube so that the nurse or physician can make assessments of pulse, respiratory rate, and temperature as often as desired without having to count the number of waves per time interval. In precarious clinical situations upper and lower bound alarms are used to alert the staff when changes occur that could require responsive action. Such systems, while serving well their purpose of continuous surveillance of the patient, produce large amounts of taped data that contain a wealth of clinical information often difficult to analyze in retrospect. Usually these data are stored until the tapes are needed for recording the data of other cases when they are erased. Little

of them have been put to use in physiologic research or applied physiology because few methods have as yet been developed for reducing the data into a condensed form that provides clinically useful information beyond that of the analog trace itself.

Recently we reported preliminarily (ref. 3) a data reduction and analytical system for the electronic impedance pneumograph. This computerized analysis provides the investigator a power spectrum of the respiratory trace from the patient over a chosen time interval. Since, as is well known, respiratory rate and amplitude can be modified by direct, as well as reflex neural pathways from other systems, changes in impedance pneumograph traces are not unique for each kind of systemic stress that modifies breathing. These changes, however, can indicate that respiratory activity is being modified by external stimuli or extra-respiratory stresses. Examples include the common ear cough that results from irritation of the sensory endings of the auricular nerve by plugs of wax in the auditory meatus; altered respiratory patterns caused by sudden immersion in cold water, painful stimuli, nausea, vomiting, muscular effort, and blood pH and gas changes. These changes in respiratory amplitude and frequency are mediated through autonomic neural elements in the various organs concerned and are presumed to be primarily of parasympathetic (vagal) origin, best described as "vagal looping."

The purpose of our study was to see if pulmonary-impedance power spectral

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analysis could be used to detect the onset and course of gastrointestinal distress induced pharmacologically or by total-body irradiation; to see how typical the computed power spectra and their variances were for such well defined respiratory states as exercise induced hyperpnea, respiratory acidosis, and hyperventilation in volunteers and in patients exposed to therapeutic levels of total-body irradiation; and, if possible, to use this system to detect radiation induced decrements in physical performance to study their relation to exposure rate.

These observations could have some medical usefulness during extended manned-space missions (e.g., orbiting platforms and interplanetary expeditions) in a potentially hostile environment. The potential hazards of space radiation (proton fluxes, heavy primaries, X- and gamma-radiations, solar activity) have been previously reviewed by others (refs. 4, 5, 6, and 7). In addition to potentially high-flux space radiation, on-board power reactors will increase the environmental background and crew exposures on extended manned space missions. While the types and intensities of space radiation are well defined, if not predictable, the response of man to these ionizing events is not well known because of the absence of experimental observations. However, the general sequence of events involved in the radiation prodrome (nausea, vomiting, fatigue) are well documented for man (refs. 6, 8, 9, and 10), but the majority of quantitatively related radiation-induced changes have been studied in lower animals where psychological testing was primarily involved (refs. 11 and 12). The effects of radiation on the performance of rats subjected to swim tests, however, have shown that exposures of 300-1000 R depressed performance ability in a dose-rate dependent manner (ref. 13). Thoma and Wald (ref. 14) reviewed the clinical signs and symptoms of radiation

accident victims and report that postexposure fatigue may be evident for 4 days to several months following exposures estimated to have been 240-600 rads to the total body. Fatigue was not measured quantitatively nor produced by objective testing; each victim described his own feeling of malaise.

A review of pertinent literature on human performance ability after radiation exposure has been published by Zellmer (ref. 15). Psychological testing of patients receiving total-body irradiation therapy has been reported by Payne (16) and demonstrates that no decrement occurs in man's ability to perform well-directed tests (e.g., USAF SAM rotary pursuit test and USAF SAM complex coordination test) after exposures of 15-50 R of X rays (0.95/min). Likewise, the same conclusions were reached after exposures of patients to 25-200 R given in 25 R fractions at 3.8 R/min. All individuals (ages 23-76 yr) exposed were being treated for malignancies (ref. 16).

Our studies, on the other hand, dealt with nondirected tests (bicycle ergometry) for assessing performance abilities during and after radiation exposure. While highly motivated individuals (e.g., trained astronauts) might be expected to demonstrate continued performance on well-directed duties even in the event of accidental incapacitating radiation exposures, their ability to perform nondirected (general activities) might be reduced. This is one question our investigation seeks to answer.

METHODS

Traces of pulmonary impedance were obtained before, during (in the case of exposure protraction), and after therapeutic levels of total-body irradiation of leukemic patients with ^{137}Cs or ^{60}Co gamma rays. The radiation facilities used have been previously described (refs. 17, 18, 19, and 20). Briefly, fractionated exposures of 30 R/day were carried out in a ^{137}Cs

total-body irradiator at a rate of 1.5 R/min, while protracted (30 R/day) and fractionated (10 R/day) exposures were administered utilizing a ^{60}Co total-body irradiator at the rate of 1.5 R/hr. An electronic physiologic monitoring system² was used to obtain the pulmonary impedance traces. Three surface (skin) electrodes were attached to the subject, one to each anterior lateral axillary line on each side of the subjects chest and over the xyphoid sternal process. The impedance of a 100 μamp current passing between the axillary electrodes is measured simultaneously with the cardiac current changes (EKG). The xyphoid electrode is the grounding circuit. This configuration of electrodes has been described previously by others using it to monitor the physiologic status of astronauts in space flight or in simulated tests (refs. 21, 22, 23, 24, 25, and 26). Impedance pneumograph traces were also obtained on a normal volunteer who ingested an emetic (ipecac); on normal unirradiated volunteers and patients (undergoing total-body therapeutic irradiation) all of whom exercised periodically on a bicycle ergometer. The voltage changes in pulmonary impedance were recorded on strip chart and on analog tape from which 4-minute data segments were selected, converted into digital form and analyzed using an IBM-1800 computer. In our system, in its present stage of development, digital data processing can be done in real time or in retrospect. After digital conversion, the data were processed with a power spectral analysis program which computed power spectral estimates and respiratory variances that were graphed automatically.

RESULTS

Selected impedance pneumograph traces obtained from a patient receiving 30 R/20

²Beckman Type R dynograph, Beckman Instrument, Inc. Palo, Alto, California.

hr day at an exposure rate of 1.5 R/hr are shown in Fig. 1. The total exposure was 250 R over an 8-day period. These traces illustrate that normal, regular breathing occurred throughout all monitoring periods. The regularity of these impedance pneumographs is reflected by low-power spectra and nonvarying frequencies as shown in Fig. 2. During the entire exposure the patient, who had received no previous radiation therapy, felt well and did not develop nausea or loss of appetite. In Fig. 3 the pre- and postexposure pulmonary impedance traces are shown for a patient who received rapidly-delivered fractionated exposures of 30 R/day (1.5 R/min) on each of 5 consecutive days for a total exposure of 150 R. The pulmonary impedance traces became increasingly irregular postexposure with increasing exposure accumulation up through day 4. The effect of the last fractional dose (30 R) appears to have been suppressed by 20 mg chlorpromazine administered prior to exposure. The changes in pulmonary impedance are more easily visualized in the power spectra computed from them (Fig. 4). All 5 postexposure pulmonary impedance traces were obtained within 30 min after irradiation. Subjective levels of postexposure gastrointestinal distress experienced by the patient are shown in Table 1. These symptoms correlate well with the strip chart traces and the changes in their power spectral reductions. There is (Fig. 4) a progressive increase in the shift of pulmonary impedance waves to lower frequency and higher amplitude and power as radiation exposure accumulates. The patient reported that recovery from the postexposure nausea, reflected by these changes, occurred 2-8 hours later. The relative absence of symptoms and pathologic pulmonary-impedance patterns and power spectra also correlated, as seen in Figs. 3 and 4, for day 5. The daily pretreatment pulmonary impedance traces and their power spectra are remarkably uniform and normal, substantiating, apparently, the patient's

claim that symptoms of radiation sickness were absent at those times.

TABLE I

PATIENT EVALUATION OF GI DISTRESS THAT FOLLOWED TREATMENT WITH 30 R (1.5 R/MIN) DAILY FOR 5 DAYS

<u>Accumulated Exposure</u>	<u>Described GI Distress</u>
Post 30 R	None
" 60 R	Mild
" 90 R	Moderate
" 120 R	Severe
" 150 R	Mild

The comparison of dose rate effects was enhanced by the fact that the patient who received the fractionated radiation therapy (see above) returned for additional radiation treatment but the exposure (150 R) was protracted (1.5 R/hr) over a 5-day period. Pulmonary impedance strip chart traces recorded before, during, and immediately after the therapeutic irradiation period indicate that respiratory alterations occurred prior to and early into treatment and consisted primarily of high amplitude (deep) breathing (Fig. 5). Power spectra of pulmonary-impedance wave forms (Fig. 6) reflect these findings and show that no significant pulmonary alterations occurred throughout exposure after the initial changes. No low-frequency components are present in the power spectra obtained in relation to this dose protraction, however, low frequency shifts did occur in this same patient when the exposure (150 R) was fractionated (see above). These findings are interpreted as being due to psychologically-induced nausea related to the severe nausea experienced previously by this same patient when given fractionated irradiation therapy 6 months prior. The fractionated exposure (150 R) which induced nausea in this experiment is well below the 300 rad dose (single exposure) reported by Lushbaugh, et al. (ref. 10) that

resulted in a mean vomiting-onset time of 144 ± 66 min. Gerstner (ref. 9) has previously indicated that nausea and vomiting, if present, will occur approximately 6 hrs after doses below 600 rads. While this particular patient may have a low radiation-induced GI distress threshold, the dose rate influence on the human radiation prodrome is illustrated.

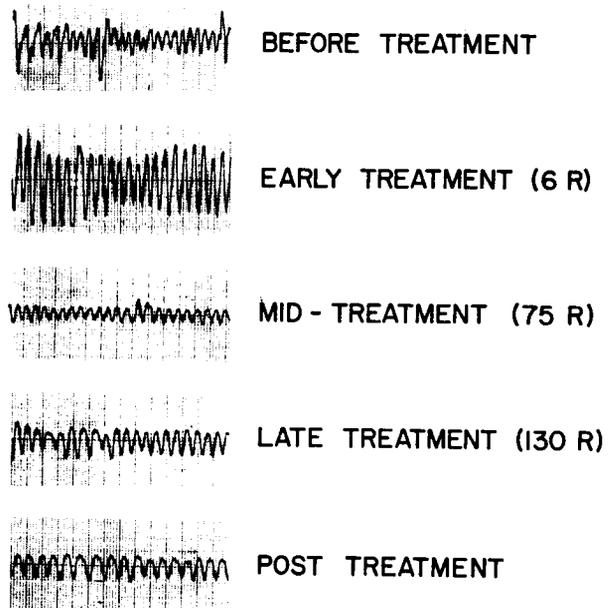


Figure 5. Pulmonary impedance tracings from patient exposed to 150 R (30 R daily) at 1.5 R/hr. Figures in parenthesis indicate accumulated R at time of pulmonary monitoring.

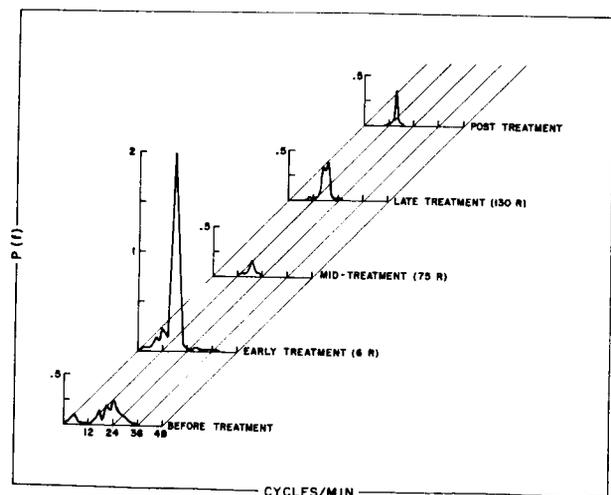


Figure 6. Power spectra of pulmonary impedance wave forms obtained at specific intervals before, during, or immediate after exposure to 150 R (30 R/day) at 1.5 R/hr. Figures in parenthesis indicate accumulated R at time of pulmonary monitoring.

In order to compare radiation and pharmacologically induced gastrointestinal distress, we obtained power spectra of pulmonary impedance wave forms from a normal male volunteer, aged 22, who was administered an emetic (ipecac). Power spectra of these pulmonary traces are shown in Fig. 7 and illustrate shifts to high-power, low-frequency components at those times when the subject experienced severe nausea (17-20 min) and when emesis occurred (49-52 and 57-60 min, respectively). These data demonstrate similar respiratory phenomena occurred (as measured by our method of analysis) in our experiments when gastrointestinal distress occurred regardless of its means of induction. The quantity of analog data obtained in this experiment encouraged us to modify the computer program to afford greater data reduction. This modification is based on the fact that the area under a pulmonary impedance power spectrum is the total variance in terms of amplitude and frequency of respiration. This single number can be computed and used as a one-dimensional expression of the level of respiratory efforts.

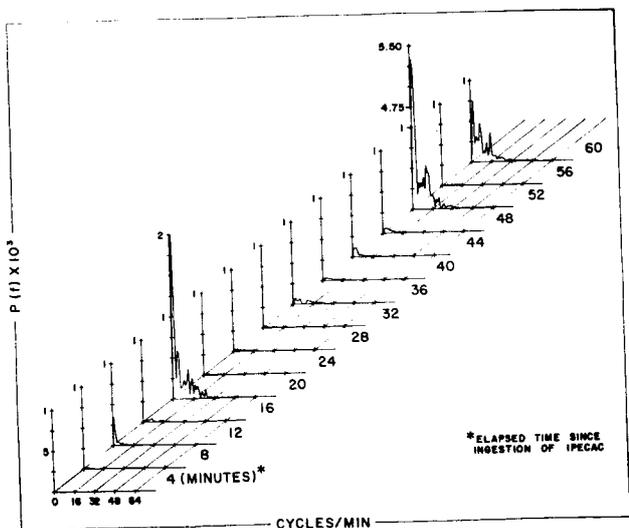


Figure 7. Power spectra of pulmonary impedance wave forms obtained over a 1 hr time period in a normal volunteer following administration of an emetic (ipecac).

When this number is plotted as it changes with time, a continuous graph is produced of the variance in respiratory effort throughout the monitoring period. This new method requires one-half the previous computing time; the output consists of two indices (a mean and the variance of the power spectrum) that can be used without graphing the individual power spectrum. In this case, the mean is the average transthoracic voltage as measured by the impedance pneumograph coupler, while the variance is directly proportional to the area under the power spectrum. The power spectrum of the pulmonary impedance wave form is not graphed in this new system unless requested by the investigator or clinician. In addition, this new method provides separate analysis of each of 4 consecutive minutes of pulmonary impedance data instead of one combined analysis of 4 minutes of data. An average mean and average variance (four 1-minute data periods /4) also is provided. We have defined the minute-by-minute variance as the continuous variance and its average over 4 minutes as the average variance.

Data obtained from the volunteer with pharmacologically induced GI distress (see above) and analyzed by the new method are shown in Fig. 8. Increased continuous variance corresponds exactly to the minute with the occurrence of severe nausea (18th min) and emesis (50th and 59th min). These changes in respiratory function are also well portrayed by the average variance which tends to smooth the data without losing fidelity. Inferences drawn from data analyzed by both the old and new methods would be the same.

We anticipated this new method would have a useful purpose in the analysis of long-term pulmonary studies and have applied it to pulmonary impedance data obtained from patients receiving total-body therapeutic irradiation, all of whom exercised on a bicycle ergometer. Figure 9 illustrates the pulmonary impedance variance obtained from a normal volunteer

before, during, and after exercising to tolerance (~ 8 min) against a work load of 75 watts. Shifts in both continuous and average variance occurred during the initial phases of exercise and increased to a maximum late in the exercise period. Post-exercise variances decreased periodically returning to preexercise levels at about 35 minutes.

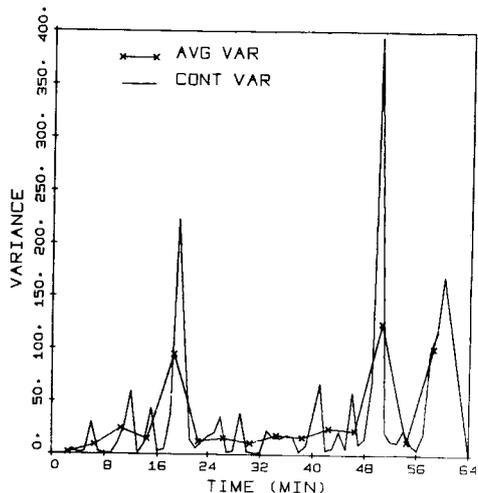


Figure 8. Time-series graph of average and continuous pulmonary impedance power spectral variances obtained over a 60 minute period in a normal subject following ingestion of ipecac.

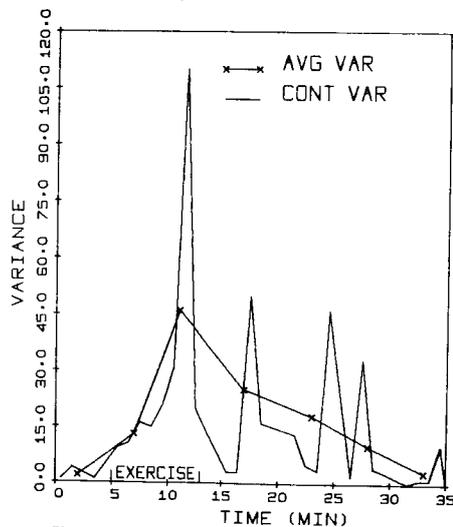


Figure 9. Pulmonary impedance variance from a normal individual obtained before, during, and after exercise on a bicycle ergometer. The exercise work load was 75 watts; pedaling speed was 60 RPM.

In order to determine the effect of total-body irradiation on performance decrement, pulmonary impedance data were obtained from selected patients receiving protracted or fractionated exposures (1.5 R/hr) and who exercised periodically before, during, and after exposure. Patients were selected on the basis of their will-

ingness and ability to exercise and that their disease was not acutely debilitating. No aspects of radiation-induced fatigue were ever discussed with these patients. Data from two patients exposed to protracted radiation therapy (30 R/20 hr day) at a rate of 1.5 R/hr are shown in Figs. 10 and 11. Only the average variance of the pulmonary impedance power spectral data is illustrated. Increased respiratory demand during and immediately after exercise was reflected by changes in pulmonary impedance wave forms in both patients studied and closely resembled changes noted in exercising volunteers. Increased power at various respiratory rates (generally >20 /min), seen as a large increase in total variance, was amplified after total-body exposures of 100-150 R. A decrement in performance ability was indicated by a greater increase in respiratory variance, after radiation, when measured at 3 and 10 days postirradiation in one patient who received 100 R (Fig. 10), and at 5 days in another patient who received 150 R (Fig. 11).

Radiation-induced performance decrement was also studied in two patients receiving fractionated exposures of 10 R daily at a rate of 1.5 R/hr and who exercised on a bicycle ergometer. The results are shown in Fig. 12. Subject A is the same individual exposed (6 months earlier) to 100 R (30 R/day) at 1.5 R/hr and who demonstrated no decrement until 3 days postirradiation. Subject B received a total exposure of 140 R (10 R/day) at 1.5 R/hr but postexposure exercise was not accomplished due to unexpected thrombophlebitis. While no postexposure performance decrement was noted, slight increases in respiratory variance did occur during exposure of both patients. The significance of these changes is not understood at this time.

These data demonstrate that pulmonary impedance power spectral analysis is capable of detecting and predicting the onset and severity of radiation-induced gastrointestinal distress. The approach also serves

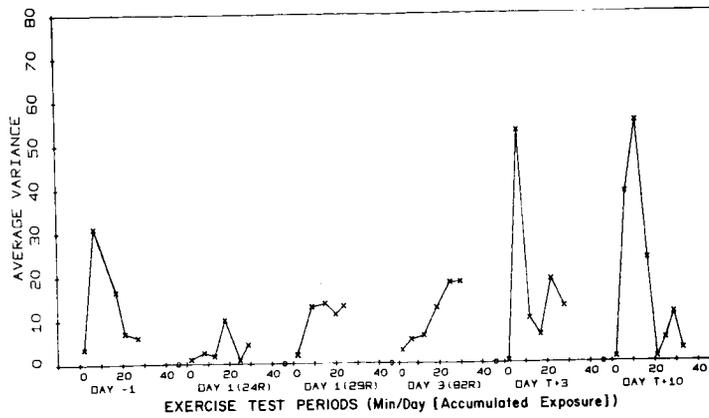


Figure 10. Pulmonary impedance variances obtained from a 62-year-old patient exercising on a bicycle ergometer before, during, and after total-body exposure (100 R) at 30 R/day (1.5 R/hr). The exercise work load was 50 watts; pedaling speed was 60 RPM. Exercise lasted 8 min for each test period.

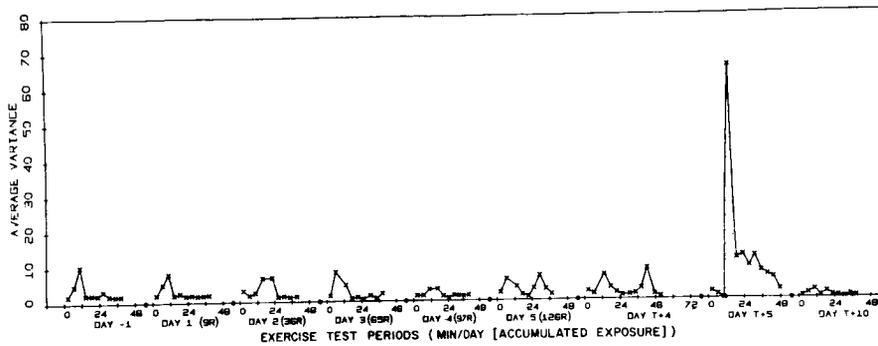


Figure 11. Pulmonary impedance variances obtained from a 65-year-old patient exercising on a bicycle ergometer before, during, and after total-body exposure (150 R) at 30 R/day (1.5 R/hr). The exercise work load was 25 watts; pedaling speed was 40 RPM. Exercise lasted 5 min for each test period.

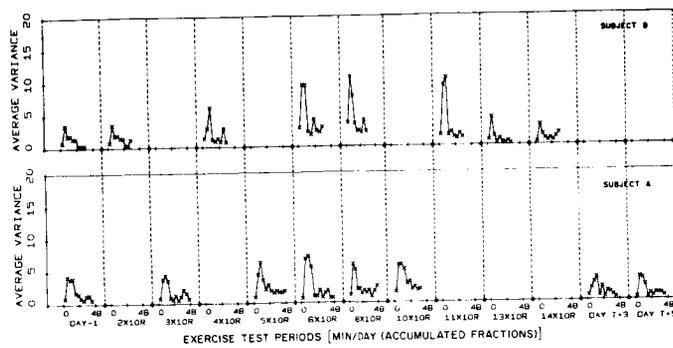


Figure 12. Treatment windows showing pulmonary impedance variance obtained from two patients before, during, and after total-body exposure to daily ^{60}Co fractions of 10 R at 1.5 R/hr. Subject A (aged 62 yr) received a total exposure of 100 R; subject B (aged 70 yr), 140 R. Each patient exercised periodically on a bicycle ergometer before and during exposure. Subject A exercised after exposure. The exercise work loads for A and B were 50 watts, 60 RPM and 40 watts, 40 RPM, respectively. Exercise lasted 5 min during each test period.

to illustrate the dose-rate influence on the human radiation prodrome and reflects the effectiveness of its chemotherapeutic control. In addition, it provides a facile means of measuring the performance decrement effects of total-body irradiation in man. The results indicate the necessity for similar studies over more extended post-irradiation time periods and a correlation of the data with biochemical changes. In experiments underway with unirradiated volunteers and with patients who receive total-body irradiation we are attempting to correlate these changes in the pulmonary impedance pneumograph during controlled exercise with levels of expired CO₂, plasma lactic acid dehydrogenase, plasma creatine phosphokinase, and plasma glutamic-oxalacetic transaminase.

SUMMARY AND CONCLUSIONS

Changes in respiratory variance revealed by power spectral analysis of the pulmonary impedance pneumogram can be used to detect and measure stresses directly or indirectly affecting human respiratory function.

When gastrointestinal distress occurred during a series of 5 total-body exposures of 30 R at a rate of 1.5 R/min, it was accompanied by typical shifts in pulmonary impedance power spectra. These changes did not occur after protracted exposure of 250 R (30 R daily) at 1.5 R/hr that failed to cause radiation sickness.

This system for quantitating respiratory effort can also be used to detect alterations in one's ability to perform under controlled exercise conditions. Performance decrement due to various stresses is difficult to quantitate because of a lack of objectivity in most tests and bias due to different levels of motivation. In our tests the end point of increased respiratory variance and the method of measuring it is too obtuse for the test subject to recognize and falsify. Increased fatigability has been reported after total-body irradiation but little is known about doses required and the time for its occurrence. Using pulmonary impedance power spectral analysis we found while observing 4 irradiated patients that increased fatigability could occur during prolonged fractionated exposures to 10 R daily and after completion of continuous exposures to 30 R/day for 5 days. The performance decrement detected by this means occurred at lower total doses than previously reported for radiation-induced fatigue and at lower exposure rates than those that cause gastrointestinal distress.

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