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Investigating Activity in Hospitalized Patients with Chronic Obstructive Pulmonary Disease: A Pilot Study

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Chronic obstructive pulmonary disease (COPD) patients commonly experience activity intolerance. However, COPD is not the single pathologic cause of this distressing physical impairment. Skeletal muscle wasting, a concomitant finding among adults with COPD, has also been identified as a significant contributor to activity intolerance, though the etiology is unclear at this time.^{1, 2} When COPD patients are hospitalized, systemic inflammation and bed rest can further aggravate activity intolerance.³ With disparate causes contributing to the COPD patient's struggle with activities of daily life, examining the molecular mechanisms behind skeletal muscle impairment offers hope for better understanding of the disease's pathology and the development of effective interventions to reduce its chronicity. One area of particular interest involves cytokines, which show promise as inflammatory molecular biomarkers linking both COPD and activity intolerance. Several cytokines contribute to the pathology underlying organ dysfunction in both lungs and skeletal muscles.

This study investigated whether selected cytokines vary between rest and activity periods in COPD patients who were critically ill. Specific aims of the study were (1) examine the serum levels of interleukin (IL)-6 and IL-10 in hospitalized patients while at rest and (2) compare "at rest" serum IL-6 and IL-10 levels with those obtained immediately after a period of therapeutic activity. This was an observational, exploratory study that had secondary aims of exploring types and duration of brief, episodic activity and the feasibility of analyzing serum outside of usual clinical laboratory procedures.

Review of the literature

Cytokines influence the onset and progression of local and systemic inflammation, have been implicated in pathology related to COPD, and can be altered by exercise.^{4–7} These small, soluble signaling proteins are produced by all nucleated cells⁸ and are grouped into families based on the presence of shared sequences of amino acids. Cytokines have been classed as pro- and anti-inflammatories, interferons, chemoattractants, and growth factors. Rarely is a single cytokine synthesized and released in isolation; generally, these molecules are released in a complex cascade. Cytokines exert their influence by attaching to a cell surface receptor and typically signaling a pathway that results in intracellular activity. Many cytokines are pleiotropic—one cytokine can have multiple effects. For example, IL-11 can induce acute phase proteins in the liver and stimulate hematopoiesis in the bone marrow.⁹ Cytokines are also characterized by redundancy—several can produce the same activity, such as both tumor

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necrosis factor (TNF) and IL-1 activating the same nuclear factor-kappaB pathway and regulate the immune response to infection.⁹

COPD is a chronic inflammatory process with tissue damage and repair processes.¹⁰ Several cytokines have been implicated in COPD pathology.¹¹ Two of these cytokines have also been studied in relationship to exercise and muscle activity: interleukin (IL)-6 and IL-10. IL-6 is a pro-inflammatory marker; IL-10 is an anti-inflammatory marker.

Interleukin-6 was originally identified as a lymphokine, a soluble factor secreted by activated lymphocytes. Now there is evidence it is expressed in all nucleated cells, especially white cells, epithelial cells, chondrocytes and myocytes.¹² IL-6 cytokine concentrations are increased in induced sputum, bronchoalveolar lavage, exhaled breath condensate,⁷ and plasma of COPD patients, especially during exacerbations.^{6, 13, 14} IL-6 is particularly relevant to patients with COPD and activity intolerance^{11, 13–15} because it has been implicated in myocyte dysfunction and skeletal muscle wasting, both of which contribute to activity intolerance.^{16, 17} Several studies suggest strenuous exercise increases IL-6 in healthy adults. However, low-to-moderate exercise does not seem to cause an increase in serum pro-inflammatory molecules in subjects with stable COPD.^{18, 19}

IL-10 is a key anti-inflammatory cytokine. Many pro-inflammatory stimulants, including IL-6, stimulate the production and release of IL-10.²⁰ Not only does IL-10 turn off pro-inflammatory cytokine production, it inhibits matrix metalloproteinases that contribute to lung tissue damage in COPD.⁶ Prolonged, strenuous activity in healthy males resulted in a 27-fold increase in IL-10 immediately after activity.²¹ Low levels of IL-10 predict decreased activity and increased angina in patients with unstable angina, but it is not clear whether low activity causes low IL-10 or low IL-10 results in decreased activity.²² In cell cultures of chondrocytes, cyclic tensile strain of a low magnitude promotes IL-10, indicating that low-to-moderate levels of activity may promote anti-inflammation response in articular cartilage.²³ In this same laboratory, high levels of strain increased inflammation, indicating that a balance between too little and too much activity has the most effect on reducing inflammation.²⁴

Low and moderate levels of activity have the potential to reset inflammatory dysfunction.^{25, 26} Restoration of inflammatory balance may lead to improved function and patient outcomes.^{5, 27} Influencing the synthesis and release of IL-6 and IL-10 may promote inflammatory balance. But first, one must examine whether low levels of activity commonly prescribed in critical care settings have any effect on serum levels IL-6 and IL-10 in selected acutely ill adults. The diagnosis of COPD exacerbation was selected to provide some homogeneity to the sample for this feasibility study and to provide much-needed information about the ability of patients with COPD exacerbation to initiate and sustain early, therapeutic mobility during hospitalization. In addition to potentially improving the inflammatory profile of patients with COPD exacerbation, early therapeutic mobility may alter the illness trajectory of patients vulnerable to activity intolerance.

Cytokines are an important component of the inflammatory cascade. Any internal or external environmental stimulus that initiates inflammation will also influence the production and release of cytokines. Many of these stimuli are common in hospitalized patients. Pathogens, wounds, invasive procedures, medications, body weight and comorbidities contribute to local and systemic levels of these small cell signaling molecules. Gender and age can also influence the type and quantity of cytokine synthesis. Other data suggest a genetic predisposition to hyperinflammation may contribute to pathology in COPD and other conditions.^{28–30} However, several studies suggest that exercise and moderate levels of activity are independent predictors of inflammatory markers in healthy adults as well as patients with chronic inflammatory disease like COPD.^{31–35} Examining whether *early* therapeutic mobility activities modulate

inflammation has not been explored in hospitalized patients. Therefore, this feasibility study was designed to test the procedures for a larger study while examining serum cytokines among critically ill patients hospitalized with COPD exacerbation before and after participation in early therapeutic mobility activity.

Methods

This study observed early therapeutic mobility activity as it occurred in the medical intensive care unit (MICU) and the medical step-down unit (SDU). The timing and duration of activity was adjusted in order to promote standardization. However, the activity was naturalistic or unstaged as it occurred during component of “routine” patient care; the specific activity was not prescribed by the study protocol.

Sample and Setting

Patients from the MICU and SDU of a 738 bed urban teaching hospital in Cleveland, Ohio with a diagnosis of “exacerbation of COPD” with or without pneumonia were the target population. The diagnosis of COPD was established by a physician prior to the patient’s admission to the hospital. Patients with multiple primary admission diagnoses (e.g., chest pain, heart failure) were excluded with the exception of pneumonia as respiratory infection is a common cause of exacerbation of chronic lung disease.³⁶ COPD exacerbation was selected as the study focus because participants were more likely to have similar immunological (and, therefore, cytokine) profiles/trajectories.³⁷ To enhance homogeneity of the sample, only patients with the selected diagnosis and a partial pressure of arterial oxygen (PaO_2) divided by the fraction of inspired oxygen (FiO_2), or P/F ratio of 100–400 were included. This P/F ratio was selected in consultation with the MICU physician director so as to capture patients with the potential to engage in a variety of physical activity; a low P/F ratio indicates high acuity. Only patients with a FiO_2 of greater than .6 were included, regardless of P/F ratio, to ensure the patient was safely able to oxygenate. Inclusion criteria also required that the first observation occur between 48 and 60 hours of admission to the unit (i.e., “early”). There were no exclusion criteria based on gender or minority status in this convenience sample. Patients received standard therapy at hospital admission, including inhaled bronchodilators, intubation and mechanical ventilation or noninvasive ventilatory support, oxygen supplementation, glycemic control, antibiotics as indicated, and continuation of home medications. The study was approved by the institutional review boards and the General Clinical Research Center at the hospital.

Study Procedure

Potential subjects were identified by the PI or a research assistant rounding daily. After obtaining informed consent from the participant or responsible decision-maker, demographic and descriptive variables were collected from bedside records and an actigraphy device was placed on the participant’s dominant wrist. The bedside nurse was consulted regarding the planned activity for the subject and a schedule of observation was negotiated. Each observation had a sequential period of rest and activity; the initial period (rest or activity) was randomly assigned with a coin toss. Rest periods had a duration of 60 minutes duration to allow stabilization of serum cytokines.³⁸ The period of rest provided baseline serum cytokine values. The goal for duration of activity was 20 minutes. Serum was collected immediately after each rest and activity period. Total observation time per subject was approximately 90 minutes: 60 minutes of rest, 20 minutes of activity, and 10 minutes of miscellaneous data collection.

The principal investigator (PI) observed all periods of rest and activity and recorded type(s) of activity, duration of rest/activity, vital signs with peripheral oxygenation values (SpO_2), and adverse events in a log. In addition, the actigraphy device was used to capture activity counts

during rest and activity (Figure 1). Activity was provided by either the bedside nurse or initiated by the subject. A standardized period of observation between 10 am and 2 pm, designed to mitigate diurnal variations in cytokines, was also congruent with hospital routines such as medication administration and visitation, minimizing potential confounding factors such as a variable drug levels.

In subjects with a second day of MICU or SDU stay and who had venous access, a second set of observations was collected as on day 1 with a randomized period of rest and activity with serum collection immediately following rest and activity. The second day of observation was conducted to determine whether the data varied from day-to-day and to characterize changes in the type and duration of activity. Activity remained under the direction of the bedside nurse.

Mobility activity was determined by the physician order and nurse providing direct care to the subject; only the time of day for activity was controlled during the study period. Periods of rest and activity occurred sequentially after initial randomization. If the patient needed an intervention (e.g., suctioning or hygiene) during observation periods and it occurred during a rest period, the rest period was restarted at the end of the intervention. Whenever possible, activity was sustained for 20 minutes. Rather than turn/reposition a patient for 20 minutes, turning was combined with range of motion. Patient fatigue, staff or patient request, or needs for other interventions were all acceptable reasons for truncating a period of activity. If a patient was able to tolerate a period of activity longer than 20 minutes, then cytokines were collected at the end of 20 minutes. Serum was collected immediately after a period of rest and after a period of activity directly observed by the PI.

Data Collection—Variables collected included admitting diagnosis, age, gender, body mass index, illness acuity, albumin, admitting unit (MICU or SDU), and medications. Illness acuity was measured with the Acute Physiology and Chronic Health Evaluation (APACHE) III form and the ratio of oxygenation to delivered oxygen (P/F ratio).³⁹ The P/F ratio was computed using the amount of documented delivered oxygen and reported laboratory value for the partial pressure of arterial oxygen nearest to the time of observed activity/rest.⁴⁰ Intra-rater reliability was established and maintained at 90% agreement for all data points collected from the chart. Patient vital signs were collected using Space Labs bedside monitor and direct observation and recorded on a log. The patient responses and safety events monitored included line dislodgement, fall, and de-saturation/de-oxygenation.

Activity was measured via direct observation and with actigraphy. Activity was defined as therapeutic mobility purposefully initiated by the nurse, bedside clinician (e.g., physical therapist, occupational therapist, or unlicensed assistive personnel) or patient to maintain joint range and muscle strength. *Early* mobility was further defined as occurring within 72 hours of admission to the unit. Therapeutic mobility was recorded in log format and with actigraphy, using a single or combined activity including

- Turning: moving the patient to a lateral, supine, or prone position from a baseline lateral, supine, or prone position;
- Range of motion (ROM): activity that repetitively positioned an extremity around a joint with or without muscular activation;⁴¹
- Dangling: activity that had the patient sit with legs hanging over the side of the bed, with or without foot, back, and arm support for a defined period;⁴²
- Chair sitting: activity that had the patient transferring to a chair after exiting the bed. It did not include sitting with a 90-degree head-of-bed elevation while still in bed; when a patient transferred to a chair, activity was considered over after the patient

assumed a quiet posture while sitting—activity was the active transfer from bed to chair.

and

- Ambulation: activity that had the patient walking with or without aid or assistive device.

Actigraphy is the use of instruments sensitive to movement, typically worn on the wrist, to record activity over time. This study used the Mini Mitter Actiwatch™ to record and store the time (duration) of movement, as well as the intensity (i.e., counts) of movement (www.minimitter.com). The device contains an accelerometer which detects motion. As the accelerometer detects motion over one minute epochs, activity counts are collected. When more activity occurs in one epoch, the number of counts increases. There is only one mode of recording, activity counts, with this device. Activity counts are displayed as both a graph (i.e., actogram, with minute-by-minute vertical lines, depicting activity) and as a number value (range 0–99,999) (Figure 1). Only the number counts were used for analysis. Activity counts were computed from 20 minutes of observed activity and 60 minutes of observed rest (Figure 1). The Actiwatch™ has a reliability of 0.92 during calibration and test-retest and has been validated with other measures of movement such as heart rate, oxygen consumption and integrated electromyography with correlations of 0.74–0.98.⁴³ Wrist actigraphy has demonstrated sensitivity and validity in measuring upper-extremity movement during pulmonary rehabilitation in COPD patients in an outpatient setting⁴⁴ and correlates well with activity in critically ill patients.^{45, 46}

All cytokines were measured in serum samples collected from existing arterial, central or peripheral intravenous catheters. Two milliliters of blood were collected immediately after activity and after rest. The serum sample was manually aliquotted into storage tubes and frozen at –70°C until the time of analysis. Samples were assayed in duplicate for IL-6 and IL-10 concentrations using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN). The General Clinical Research Unit at the hospital stored samples (*GCRC M01RR000080*). Serum samples were analyzed in a research lab familiar with the assay. The detection limits of the ELISAs ranged from 1–300 pg/ml for IL-6 and 1–100 pg/mL for IL-10. The sensitivity for this product for both IL-6 and IL-10 was 0.5 pg/mL.

Analysis of Data

Demographic data were summarized with means for continuous data and percentages for categorical data as appropriate. Values of IL-6 and IL-10 at rest and after activity were examined with the Wilcoxon signed rank test for paired samples, given the small sample size and non-normal distribution of cytokine values and with repeated measures multiple analysis of variance (RM-MANOVA) for effect size. Activity was described as type (mode), duration and the averaged activity counts from the Actiwatch™ software during the observation period. Data were entered into SPSS (v.15) for analysis.

Results

Sample

A total of 17 subjects were enrolled. The sample was 82% female with an average age of 60 + 9 years, obese, with moderately severe illness and two comorbidities (Table 1). All subjects were invasively or noninvasively mechanically ventilated at the time of the first observed activity period. Eight subjects had a second set of paired data at rest and after activity on day 2 after enrollment; nine subjects were discharged or unable to contribute a second set of blood samples. No subjects experienced an invasive procedure such as line placement or changes in

ventilator settings, within 3 hours before activity observations. No subjects experienced changes in medications on the days of observation; no tapering of glucocorticoids or addition of anti-inflammatories occurred around the observation periods. All enrollees received a glucocorticoid; Table 2 lists medications given to patients in this sample.

Therapeutic Mobility Activities

The average duration of activity was 18.8 minutes on day 1 for 16 subjects. One subject declined to participate in therapeutic mobilization on day 1. All 8 subjects participated for 20 minutes on day 2. Activity for the 8 subjects studied over two days showed progression of therapeutic mobility: on day 1, no subjects walked and on day 2, 6 subjects were able to walk at least a short distance. The types of therapeutic mobility activity observed are summarized in Figure 2.

Actigraphy Results

Subjects wore actigraphy devices for 24 to 48 hours, beginning with enrollment in the study. Only activity counts for the period of direct observation (up to 20 minutes of therapeutic mobility and 60 minutes of rest) were used for this analysis; all activity counts indicated a constant, low level of activity with averaged counts ranging from 6 to 396 changes as detected by the accelerometer during observations. The mean number of activity counts was 98 on day 1 and 124 on day 2 during observed activity, a difference that was not significant. There were no significant differences in activity counts, comparing day 1 to day 2 ($t = -.654$; $p = .5$). Actigraphy values obtained during 60 minutes of rest were about 50% of the averaged values during therapeutic mobility activities with a mean of 45 on day 1 and 68 on day 2).

Cytokine Results

The IL-6 and IL-10 values at all time points were variable. Nonparametric tests indicate no differences between IL-6 at rest and IL-6 after activity or IL-10 at rest and after activity (Table 3). Examining graphic displays (Figure 3), trends suggest no change in IL-6 on day 1 and a decrease in IL-6 after activity on day 2 when compared to rest. IL-10 decreased after activity on day 1 and increased after activity on day 2.

Cytokine data were used to calculate an effect size using partial eta squared from repeated measures MANOVA. The effect size for the changes in IL-6 from rest to activity was .17 (small-to-moderate). The effect size for changes in serum IL-10 was .26 (moderate). This effect size can be used for future studies to calculate sample size.

Additional Findings

All subjects maintained SpO₂ within 2% of baseline during activity and there were no episodes of peripheral hypoxia. The mean SpO₂ was 96% at rest (range 86–100%, standard deviation [SD] 3.9) and during activity was 94% (range 84–100%, SD 2.7). The average PaO₂ prior to activity in this study was 71mmHg. There were no episodes of >20% variation in heart rate, systolic or mean blood pressure, or respiratory rate during activity compared to resting values. No adverse events such as a fall or line dislodgement occurred during data collection.

Discussion

IL-6 in normal individuals ranges from 1–5 picograms/milliliter (pg/mL).¹⁹ Among COPD patients in outpatient settings, IL-6 at rest has been reported in ranges from 2.88–9.45 pg/mL. 47–49 IL-10 in normal individuals ranges from 0–10 pg/mL.⁵⁰ In community-dwelling patients diagnosed with COPD, plasma IL-10 ranges from 2.12 to 8.19 pg/mL.⁵¹ The hospitalized subjects in this study showed elevated serum IL-6 values similar to patients with

COPD, with resting IL-6 averaging 10.8 pg/mL over both days. Values for IL-10 were significantly elevated, averaging 32 pg/mL at rest on day 1 and 16.9 pg/mL on day 2.

This study was not designed to detect significant differences between cytokines obtained after rest and after activity, but to explore the feasibility of measuring two cytokines in association with observed rest and activity. Data suggests that the differences in cytokines are variable and calculations of effect sizes indicate the need for a relatively large sample size to determine if 20 minutes of activity alters these inflammatory biomarkers. Previous studies about changes in cytokines with exercises in community-dwelling adults with COPD have conflicting results. In two studies, after intensive or maximal exercise in COPD patients, plasma biomarkers of inflammation were not elevated, although lack of significance may have been influenced by the small sample sizes (i.e., $n = 20$ and 15 , respectively).^{19, 52} Subjects in one study were characterized by low levels of IL-6 at baseline (i.e., 5.68 pg/mL) and more severe baseline hypoxemia with an average $\text{PaO}_2 < 66$ mmHg and a SpO_2 of $< 93\%$ compared to this sample.¹⁹ Both the low baseline serum IL-6 and increased hypoxia may influence the production of cytokines after exercise or activity.

In two other studies, markers of inflammation, including IL-6, were elevated after a program of rehabilitation in COPD patients. Baseline IL-6 was low (5.62 pg/mL) but oxygenation was close to the values for this report (PaO_2 mean of 69 mmHg).^{18, 53} Again, both of these studies had small sample sizes (i.e., 18 and 10 , respectively).

Numerous factors, such as dosage of glucocorticoids, changes in ventilatory support, and obesity, can affect serum cytokine levels. However, in this study, changes in medication, ventilatory settings, nutrition, and body weight were unchanged during activity periods and serum collection, suggesting that subjects can serve as their own controls in a larger clinical trial. In addition, the study's observations suggest that hospitalized COPD patients can engage in activity periods of 20 minutes duration and that, in many cases, progressive activity (increased time and intensity) over a 24-hour period is possible for these patients.

The potential benefit of progressive activity for COPD patients receiving mechanical ventilation is an interruption of local and systemic inflammation, promoting recovery. There is evidence that pulmonary rehabilitation (defined as exercise training for at least 4 weeks) contributes to clinically important changes in activity tolerance and muscle function.⁵⁴ In addition, there is some evidence that physical performance during hospitalization is a better predictor of disability than a pre-event self-report of functional limitations among older adults.⁵⁵ Given the benefits of exercise and progressive mobility in patients with stable conditions, further exploration of the risks and benefits of early therapeutic mobility in preserving function and supporting recovery during acute exacerbation of COPD is warranted. Future studies should examine multiple periods of early progressive mobility and patient responses over the course of hospitalization.

Limitations

The measurement of cytokines at 2 time points does not indicate chronic immune activation. However, this project was not designed to investigate the activation of the immune system over time but, rather, over a single intervention that commonly occurs in acute care settings. Challenges in collecting blood samples from critically ill adults, processing the serum samples, providing a consistent duration of activity and evaluating the subject's systemic response were examined and solutions were developed to plan for a larger-scale research project.

Age, gender, obesity, nutritional status, medications, comorbidities and mechanical ventilator settings may have had an effect on the ability of subjects to synthesize or release cytokines IL-6 and IL-10. For example, glucocorticoids are anti-inflammatory, and high tidal volume

settings can cause increases in pro-inflammatory cytokines in bronchial secretions.⁵⁶ However, since both medications (type and dosage) and ventilator settings were consistent during the periods of observation, changes in serum values are less likely to be the result of changes/additions to the treatment regimen. The only intervention that occurred during the observation period was activity, so each patient served as her/his own control for the variables of age, gender, nutritional status, medications, and support of ventilation. Future studies may benefit from the inclusion of comparative data, such as repeating baseline rest and activity serum collection during different times of the day to better understand physiologic versus induced changes in serum cytokines.

Conclusion

This study examined the early occurrence of therapeutic mobility activity among COPD patients during hospitalization for exacerbation with high acuity and if low intensity mobility activity contributes to changes in selected serum cytokines. Results from the study suggest that activity can occur for about 20 minutes early during hospitalization in this acutely ill sample and that it can progress over 2 days in an ICU or step-down setting. Although the physical activity was low in intensity as measured by actigraphy, it was measurably different than rest or bed rest. Further, although differences in inflammatory biomarkers were not significant in this small sample with variable activities, trend data (Figure 1) indicated that low-intensity activity has the potential to alter the inflammatory profile of hospitalized critically ill adults. Future investigations need to include more than a single episode of activity to better understand the interactions between therapeutic mobility activity and inflammatory factors. Determining the source of cytokines (i.e. white blood cells, skeletal muscles, or joints) also has value in understanding how inflammatory cytokines during acute illness contribute to activity intolerance. Future research should link progressive mobility protocols with patient outcomes, using a concise, comprehensive approach to assess the impact of interventions on individuals with COPD and critical illness.^{57, 58}

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Figure 1.
Exemplar of Actogram with excerpt of Activity Counts

Figure 2.
Activities by category, Day 1 and Day 2

Figure 3.
Cytokine Values

Table 1

Sample Characteristics N= 17

Variable	Finding
Admitting Diagnosis	COPD exacerbation --15 subjects COPD exacerbation with pneumonia --2 subjects
Gender	82% female (n = 14)
Admitting Unit (MICU or SDU)	53% from MICU
Age (mean, in years)	60 (range 35–74) SD 8.8
Illness Acuity	
Modified APACHE III	39 (range 13–69) SD 14.4
P/F ratio (mean)	307 (range 120–790) SD 150.8
Number of comorbidities (mean)	2 (range 0–4) SD 1.4
Body Mass Index (BMI, mean kg/m ²)	38 (15.8–87.3) SD 17.0

MICU= medical intensive care unit; SDU= step-down unit; mg/dL= milligrams per deciliter; SD = standard deviation; APACHE III = Applied physiology and chronic health evaluation, version 3; P/F ratio = partial pressure of arterial oxygen (PaO₂) divided by the-fraction of inspired oxygen (FiO₂)

Table 2

Medications administered within 24 hours of early therapeutic mobility activity

Category	Medications and 24-hour dose	Number of subjects receiving this drug and dose
Drugs known to affect inflammation	Prednisone 60–240 mg daily	17
	Propofol (continuous drip at 15 mg/hour)	2
	Insulin sliding scale 10–50 units daily	3
	Metformin 250–500 mg daily	2
	Glipizide 10 mg daily	1
	Flunisolide 25 mcg nasal spray daily	3
	Atrovastatin 10–20 mg daily	4
Drugs with some anti-inflammatory properties	Heparin 10,000 units subcutaneously in divided doses	4
	Low dose aspirin (81–325 mg daily)	4
	Inhaled ipatropium	12
	Ceftazidime 2 grams daily	2
	Zosyn 15.5 mg daily in divided doses	5
	Azithromycin 500 mg daily	4
	Moxifloxacin 400 mg daily	4
	Metoprolol 20–40 mg daily in divided doses	4
	Atenolol 50 mg daily	1
	Isosorbide 50 mg daily	1
	Multivitamin 1 tablet daily (antioxidant)	4
Miscellaneous drugs	Famotidine 40 mg daily	4
	Omeprazole 40 mg daily	4
	Furosemide 20–100 mg daily	3
	Hydrochlorothiazide 25–50 mg daily	3
	Lisinopril 20–40 mg daily	4
	Pramipexole 0.125 mg nightly	1

mg = milligram; mcg = microgram

Table 3

Differences between IL-6 at rest and after activity; IL-10 at rest and after activity; Wilcoxon signed ranks for related samples

	IL-6 after rest - IL-6 after activity <i>Day 1</i>	IL-10 after rest - IL-10 after activity <i>Day 1</i>	IL-6 after rest - IL-6 after activity <i>Day 2</i>	IL-10 after rest - IL-10 after activity <i>Day 2</i>
Z score (significance)	.415 ($p = .678$)	.178 ($p = .859$)	1.245 ($p = .213$)	1.413 ($p = .158$)